BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045113
Article Type:	Original research
Date Submitted by the Author:	30-Sep-2020
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Keywords:	INFECTIOUS DISEASES, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis

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ABSTRACT

OBJECTIVES: Respiratory infectious disease outbreaks pose a threat for loss of life, economic instability, and social disruption. We conducted a systematic review of published econometric analyses to assess the direct and indirect costs of infectious respiratory disease outbreaks that occurred between 2003 and 2019.

SETTING: Respiratory Infectious disease outbreaks or public health preparedness measures or interventions responding to respiratory outbreaks in OECD countries (excluding South Korea and Japan) so as to assess studies relevant to the European context. The cost-effectiveness of interventions was assessed through a Dominance Ranking Matrix approach. All cost data were adjusted to the 2017 Euro, with interventions compared to the null. We included data from 17 econometric studies.

PRIMARY AND SECONDARY OUTCOME MEASURES: Direct and indirect costs for disease and preparedness and/or response or cost-benefit and cost-utility were measured.

RESULTS: Overall, the economic burden of infectious respiratory disease outbreaks was found to be significant to healthcare systems and society. Indirect costs were greater than direct costs mainly due to losses of productivity. With regards to non-pharmaceutical strategies, prehospitalization screening and the use of protective masks were identified as both an effective strategy and cost-saving. Community contact reduction was effective but had ambiguous results for cost saving. School closure was an effective measure, but not cost-saving in the long term. Targeted antiviral prophylaxis was the most cost-saving and effective pharmaceutical intervention.

CONCLUSIONS: Our cost analysis results provide evidence to policymakers on the cost-effectiveness of pharmaceutical and non-pharmaceutical intervention strategies which may be applied to mitigate or respond to infectious respiratory disease outbreaks.

ARTICLE SUMMARY

Strengths and limitations

- A comprehensive approach was followed, and the assessment of data quality indicated that the majority of the studies included were of high quality.
- The synthesis of the results was performed using the DRM approach, which allowed for a direct comparison of the cost-effectiveness of each intervention to the null intervention.
- Costs and resources varied between different countries, different regional settings, and over time, making the cost component comparison of cost-effectiveness measures complex to interpret.
- We only focused on EU and OECD analogous countries excluding Japan and South Korea, and hence our cost-effectiveness analyses are not applicable to other countries or middle- and low-income countries.
- Discrepancies in context and populations likely affect the implementation and efficacy of interventions.

MAIN TEXT

INTRODUCTION

Emerging, re-emerging and endemic respiratory and influenza-like infectious diseases represent a threat for loss of life, economic instability and social disruption as they can rapidly spread within communities and across countries, affecting the whole globe. Annually, it is estimated that 5–15% of the population will suffer from influenza-related respiratory tract infections, while 3–5 million people face severe illness due to influenza.[1] In 2018, a total number of 109.5 million influenza virus episodes were identified among children under five years globally, with approximately 34 800 overall deaths. In Europe, seasonal influenza is estimated to lead to 4 -50 million symptomatic cases, and 15,000 – 70,000 deaths annually, however this may differ between years, as the severe 2017/2018 influenza season led to an estimated 152,000 deaths in Europe alone[2,3]

In order for robust national preparedness systems and response strategies to outbreaks to be established in the Europe, it is crucial for public health officers to receive recent evidence of the health impact and the economic burden of respiratory infectious disease outbreaks in contrast to emergency response and preparedness actions, so as to ensure well-informed decisions regarding the proper allocation of resources. [4,5] To this extent, although there is substantial evidence of the value of public health emergency preparedness previously published systematic reviews either refer to an older timeframe[6] or use mathematical models to predict the effectiveness and cost-effectiveness of measures to help inform policy decisions[7] hence there is limited recent information on the economic evaluations of pandemic and seasonal influenza control that provide an overview of the cost effectiveness of response measures.[8]

Within the above context, the aim of this systematic review of econometric analyses is to assess the economic impact of response and preparedness measures when contrasted with the cost of infectious respiratory disease outbreaks. We further synthesize the cost-effectiveness for each intervention using a Dominance Ranking Matrix (DRM) approach.

METHODS

Search strategy and selection criteria

A comprehensive systematic literature review of published econometric analyses was conducted between July-August 2019 using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[9] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[10] to identify peer-reviewed articles using two biomedical literature databases (PUBMED and EMBASE) and two economic literature databases (ECONLIT, IDEAS REPEC). The complete search strategy and search terms is available in **Appendix 1**.

The inclusion criteria were as follows:

- ✓ Exposure: Respiratory Infectious disease outbreaks or public health preparedness measures or interventions responding to respiratory outbreaks in OECD countries (excluding South Korea and Japan) so as to assess studies relevant to the European context.
- ✓ Comparator: i) No intervention (cost of inaction) or current practice, ii) Cost of preparedness vs cost of response (for studies reporting cost and benefit of public health preparedness)

- ✓ Outcome measures: direct and indirect costs for disease and preparedness and/or response or cost-benefit and cost-utility. Typical outcome measures of economic evaluations included: Life years gained or cost per life-year gained with the intervention under investigation when incremental costs are combined, cost per Quality-Adjusted Life Year (QALY) gained, cases averted, monetary outcomes
- ✓ Perspective: All direct and indirect costs pertaining to all relevant perspectives (e.g. individual, hospital, insurance and societal- including national and regional) and All direct and indirect costs pertaining to all relevant perspectives according to York Health Economics Consortium (health system perspective, including hospital, public health units; societal perspective; governmental perspective)[11]
- ✓ Study designs: All relevant analytical epidemiological designs which estimate cost either as full economic evaluation studies, including cost-minimization, cost-effectiveness, cost-utility and cost-benefit studies; cost-outcome and economic modelling studies; or partial economic evaluations;
- ✓ Timeframe: From 2003 until August 2019, to reflect the timepoint from the 2003 SARS outbreak and onward[12]

Studies that met the above inclusion criteria but did not report or perform any econometric analysis were excluded.

Data analysis and extraction

Studies identified from the searches and were uploaded into a bibliographic database in which duplicate entries were removed. Initially, a pilot training screening process was used, where a random sample of 100 titles and abstracts were screened independently for eligibility by four reviewers (KN, KZ, RP, JLB) to enable consistency in screening and identify areas for amendments in the inclusion criteria. Following this, a random sample of 50% of titles and abstracts was screened independently by two reviewers. Since a high measure of inter-rater agreement was achieved (percentage agreement > 88·7% and/ or Cohen's Kappa >0·646), the remaining titles and abstracts were screened for eligibility by one reviewer. Where insufficient information was available in the title and abstract to make a decision, the full-text article of the document was retrieved for further inspection. Full-text documents of potentially eligible studies were retrieved for the records marked for inclusion. All full-text documents were independently double-screened by two reviewers, and inter-rater agreement measures were calculated at 88·3%. Disagreements in every step of the process were subsequently discussed and agreed upon. Documents that passed the inclusion criteria on the basis of the full-text screening were included in the current review.

Appraisal of methodological quality

For evaluating the methodological quality of the final studies included in the review, the Consensus on Health Economic Criteria (CHEC)[13] checklist was used. This specific tool has been designed for the assessment of full economic evaluations and includes 19 items (questions) with answers of "Yes" or "No". For each positive answer on full economic evaluation studies, a single point was being assigned for the methodological quality, with a maximum score of 19. For the quality appraisal of partial economic evaluations, we used items from the CHEC checklist that were applicable – hence the maximum score was 16. The quality appraisal process was completed by two reviewers, with a percentage of agreement in the three pilot studies, initially assessed by both, of 837%.

Comparative economic analysis approach

All cost data were adjusted to a common currency (Euro in 2017) and price year; these data were adjusted using the Campbell and Cochrane Economics Methods Group–Evidence for Policy and Practice Information and Coordinating Centre cost converter.[14] We adjusted the original estimate of cost from the original price year to a target price year of the Euro in 2017 (€^{2017}), using a Gross Domestic Product deflator index (GDPD), obtained from the International Monetary Fund World Economic Outlook Database GDPD index data set.[15] Subsequently, we converted the price-year adjusted cost estimate from the original currency to €^{2017}, using conversion rates based on Purchasing Power Parities (PPP) for GDP. (The 2017 implied conversion factor was USD 1 = € 1·13, the €^{2017} conversion factor is €1= 1·2 USD, while with regards to British pounds, the conversion factor was £1 = € 0·88). PPP values adjust appropriately for differences in current price levels between countries, thus allowing comparisons based on a common set of average international prices; this is an advantage over pure exchange-rate conversion and GDP per capita approaches as PPPs eliminate differences in price levels between countries in the process of conversion. For studies that did not state the year of cost calculation, the costs were calculated one year before the publication year.

Synthesis of cost-effectiveness

In order to synthesize the cost-effectiveness results, the Dominance Ranking Matrix (DRM) was used, which is a classification system developed for summarizing and interpreting the results of economic evaluations in systematic reviews.[16] The DRM is a three-by-three matrix with the following classification options:

(a) Strong dominance for the intervention when the incremental cost-effectiveness measure shows the intervention as: (i) more effective and less costly; or (ii) as effective and less costly; or (iii) more effective and equal cost.

(b) Weak dominance for the intervention when the measure shows the intervention as: (iv) effective and equally costly; or (v) more effective and more costly; or (vi) less effective and less costly.

(c) Non-dominance for the intervention when the measure shows the intervention as (vii) less effective and more costly; or (viii) less effective and equally as costly; or (ix) as effective and more costly.

Within our DRM only studies that compared interventions to no intervention were included in the matrix.

RESULTS

The initial study search yielded 20 513 studies after removal of the duplicates and according to the specified selection criteria of which only 66 met the inclusion criteria after the completion of the abstract review process and were further assessed for eligibility via full text. Through the assessment of the full-texts, 52 studies were excluded for the following reasons: inadequate data on costs and/or cost-effectiveness (n=2), they were reviews (n=15), not referring to respiratory outbreaks (n=29), not referring to outbreaks of infectious diseases (n=2) and conference abstracts with no full text available (n=4). Additionally, three full-text papers were identified through the screening of the reference lists of the selected manuscripts, and hence, a total number of 17 econometric studies were considered in our analysis. The flowchart of the study selection process is presented in **Figure 1.**

Overall, 11 out of the 17 studies were of high methodological quality (>80%), five were categorized as of good quality (60%-80%), and only one was of medium quality (40%-60%). It is important to note that for the studies where a partial economic evaluation was performed, we only performed calculations for the items of the quality appraisal tool that were applicable. In general, the methodological strength of the studies was impacted mostly by inadequacies on the included costs and insufficiencies regarding the sensitivity analysis and ethics, along with non-existence of discounting and the incremental analysis in the full economic evaluation studies. **Appendix 2** presents the overall quality appraisal score, for studies related to cost of infectious disease outbreaks, and for sources related to preparedness, preventive and response measures concerning infectious disease outbreaks. The quality appraisal of partial and full economic evaluation studies respectively is in **Appendix 3 and Appendix 4** respectively.

Comparative cost analysis of infectious respiratory disease outbreaks

Regarding infectious respiratory disease outbreaks, six studies were included.[17–22] All studies referred to influenza as the disease, either relating to pandemic H1N1 or seasonal Influenza B. Geographically the studies were performed in the USA[18], Spain[17,21], France[20], New Zealand and Australia[19,22]. Five out of the six studies were observational in design (cross-sectional or retrospective) and used collected data[17,19–22]; one study was based on a simulation model[18]. Similarly, five out of the six studies assessed costs from a healthcare system perspective[17–19,21,22]; however, societal (n=3)[17,18,20] governmental (n=1)[18] and payer (n=1)[20] perspectives were also assessed. Discounting in costs was not necessary for any of the included studies as the timeframe was less than one year for all the studies, and sensitivity analyses were performed in only two studies[20,22]. A detailed description of the characteristics of the included illness studies is presented in **Appendix 5**.

Table 1 presents an analytical overview of the direct and indirect costs associated with influenza outbreaks. Direct costs mainly refer to medical and healthcare costs related to the outbreaks, along with the costs of response. Indirect costs mostly were loss of income, loss of business, and loss of productivity. The overall direct costs reported in the studies where calculated at the patient level where possible.

The most recent study was a simulation study by Prager et al.[18], in which multiple scenarios were assessed through simulation models for the US population so as to estimate the total economic burden of pandemic influenza outbreaks in the US, taking into account both the scenario of an adequately vaccinated population and the opposite. The results indicated that medical expenditures for a pandemic influenza outbreak could reach 83·2 billion, €[2017] in the no vaccination scenario, and 67·3 billion €[2017] in the vaccination scenario with vaccination subsequently having a clearly positive effect. Notably, for indirect cost estimations vaccination in a pandemic scenario would reduce workday losses by 22·2 million days, when compared to no vaccination.

Silva et al. (2014)[20] focused on an influenza outbreak in France between 2010 and 2011 and extrapolated the results to the entire country with a hypothetical approximate number of 2 million influenza cases (3·2% of the French population), for which they calculated an overall cost of 151 million €[2017] for the French Health Insurance System. Direct costs per patient ranged between 35·26 €[2017] and 73·91 €[2017], with higher indirect costs of 97·88€[2017] per day due to absence from work, for those 15-65 years old.

Two studies assessed the cost of an influenza outbreak from an intensive care unit (ICU) and hospital perspective.[18, 21] One focused on intensive care unit (ICU) and hospital costs derived from an influenza pandemic in 2009 in New Zealand among 1224 cases, according to which 122 were admitted to ICUs, surpassed 40·8 million €[2017]at an average cost of 32 167 €[2017]per patient, with significantly increased costs for patients with comorbidities.[22] The mean total hospitalization cost (normal and ICU) per case surpassed 53 553 €[2017]. Similarly, in a study that included 762 H1N1 cases from both Australia and New Zealand, the mean cost of the ICU patient was 61 368 €[2017], with a per-day cost of 4 767 €[2017].[19] On the contrary, the non-ICU patient had a mean cost of 10 755 €[2017], however, overall non-ICU patient costs surpassed those of ICU patients (12·96 Million €[2017] vs 6·1 million €[2017]), leading to a total hospitalization cost of 19·3 million €[2017] for the 2009 influenza outbreak.

Similarly, Rodriquez-Rieiro et al. (2009)[21] studied the hospitalisation costs occurred during the 2009 influenza pandemic in Spain, which reached 36·7 million €[2017] for 11 449 hospitalisations– during which the appearance of comorbidities led to higher average costs per patient (2 205 €[2017] vs 1 172€[2017] respectively). Specific populations in Spain were assessed by Morales-Suárez-Varela et al. (2016)[17] who estimated direct cost for medical visits, medication and diagnostic tests at €3 908 €[2017] for non-pregnant women and 2 227€[2017] for pregnant women of reproductive age, with indirect costs estimated at 107€[2017] and 64 €[2017] respectively.

Cost-effectiveness studies of measures in averting and/or responding to infectious respiratory disease outbreaks

We identified 11 studies[23,24,33,25–32] referring to *preparedness, preventative and response measures*, to influenza outbreaks, presented in detail in **Appendix 6**. Two studies were observational (based in the Netherlands and the UK)[23,24], and the remaining nine were simulation models (four US models, with one study each modelled for Canada, France, Australia, Israel and one referred to developed countries in general). All included studies either used a cost-effectiveness or a cost-utility economic evaluation approach. The studies' timeframes ranged from 2004 to 2018. Regarding the perspective for the direct and indirect costs, a healthcare system or society approach was consistently chosen, with only one study having an additional governmental aspect.

The preparedness, preventive and response measures described included three pharmaceutical only interventions (vaccination as a response measure, general vaccination, antiviral drug therapy and stockpiling)[31–33], four non-pharmaceutical interventions (screening at the point of contact, community contact reduction, volunteer isolation/quarantine, school closure and the use of personal protective measures)[23–25,29] and four combined pharmaceutical and non-pharmaceutical interventions[26,27,29,30]. **Table 2** presents the details of the cost-effectiveness studies on preparedness and response measures for infectious respiratory disease outbreaks. Further details on the comparative analysis of health indexes gained when adverting or responding to respiratory outbreaks can be found in **Appendix 7.**

With regards to studies that compared multiple interventions, a simulation model of pandemic influenza in the USA that studied the cost-effectiveness of stockpile strategy identified that expanded adjuvanted vaccination seemed to be the most cost-effective strategy, averting 68% of infections and deaths and gaining 404 303 QALYs at $10 844 (€9 600 €[2017]) per QALY gained relative to the stockpiling strategy.[31] Sauders-Hastings et al. (2017)[26], using a simulated population of 1·2 million reflective of Ottawa, Canada, performed a cost-effectiveness analysis of six interventions including vaccination, school closure, antiviral prophylaxis and other measures. The authors concluded that vaccination, followed by other interventions was the most cost-effective intervention compared with comparative interventions while the least cost-effective appeared to be school closure in conjunction with community-contact reduction, personal protective measures, voluntary isolation and quarantine. In particular, the cost per life-year saved estimated to be $2 581 (1 700, €^{2017}) for combined vaccination and antiviral treatment, while an estimated cost of $260 472/life-year saved (€171 590 €^{2017}) risen for school closure in conjunction with other interventions. Finally, Halder et al. (2011)[27] aimed to evaluate the cost-effectiveness by performing an individual-based simulation model on a range of interventions to determine, through a societal perspective, the most cost-effective strategies suitable for a future pandemic with H1N1 2009 characteristics, in Australia. The results showed that the strategy with the lowest cost was the dual strategy of individual school closure for two weeks along with antiviral drug strategies with a total amount of approximately AU$632 (376·31€^{2017}) per case averted. The strategy with the highest cost was the dual strategy of school closure along with the continuous – 50% workplace closure, with a cost of $103 million (61·3 million€^{2017}), per 100 000 population.

Comparative cost-effectiveness analysis

A Dominance Ranking Matrix (DRM) approach presented in **Figure 2**. These interventions include both pharmaceutical measures and non-pharmaceutical measures. The interventions were compared to the "no intervention" scenario, with the exception of one study[29] in which the comparators were vaccination vs school closure, which was subsequently excluded from the DRM. In this study using a simulated student population in the US comparing vaccination to self-isolation, concluded that self-isolation is incrementally more cost-effective than vaccination, especially for higher levels of compliance, with vaccination more cost-effective at lower rates, although both are considered as effective measures.[29]

Pharmaceutical measures

Vaccination as a response measure

With the application of our inclusion and exclusion criterea four studies assessed vaccination as a response measure in the context of an outbreak and included a cost analysis. Overall, as highlighted in the majority of the studies, this intervention was noted to have a more significant clinical effect than comparators and was more cost-saving in most cases. According to Sander et al. (2009)[30], the expanded adjuvant vaccination contributed to 404 030 QALYs making it the most clinically effective intervention compared with no intervention. Similarly, Khazeni calculated that with expanded adjuvanted vaccination, 45 941 deaths would be averted.[31] Additionally, Saunders-Hastings et al. (2017)[22] concluded that the most cost-effective approach for controlling a pandemic was vaccination in combination with antiviral therapy and prophylaxis. However, a review of the results showed that much of the cost-effectiveness of pharmaceutical interventions were driven by vigorous vaccination campaigns, while antiviral drugs' contribution was not of important significance. Finally, Madema et al. (2004)[33] through a simulation model of an influenza pandemic among developing countries calculated the costs and assessed the effectiveness of two types of vaccines, an egg-based and a cell culture-based, in comparison with no intervention. Overall, vaccination was more cost-effective than no intervention; however, vaccination with cell culture-based vaccines was the most cost-effective strategy with a cost of 3 779 €^{2017} per life-year gained. General vaccination was assessed by Sander et al. (2009)[30], who noted it to be both more cost-saving and effective than the unmitigated pandemic scenario, although when comparing prevaccination with low-efficacy vaccines with full targeted antiviral prophylaxis, it was less effective and more costly.

Antiviral drugs

Antiviral drug strategies were assessed in five studies, where it was noted that they were both more effective and cost-saving than the no intervention scenario, primarily when used as targeted prophylaxis. According to Halder et al. (2011)[27], antiviral drug strategies such as antiviral treatment and antiviral treatment in combination with household confinement and extended prophylaxis can result in reduced attack rates of 7.6% and 3.5% in comparison to the unmitigated attack rate of 13%. The costs of these strategies are also lower than the cost of no intervention.

Moreover, the cost-effectiveness of antiviral treatment, long-term pre-exposure prophylaxis and short-term post-exposure prophylaxis compared to no intervention found that therapeutic treatment and postexposure prophylaxis for exposed individuals (targeted prophylaxis) were shown to be the most cost-saving.[32] Consistent with the above, antiviral therapy in combination with a layered non-pharmaceutical approach, seemed to reduce the overall economic costs the most and it was more effective compared with no intervention.[26] Furthermore, it was noted that expanded antiviral prophylaxis could help delay a pandemic mainly when additional strategies are implemented, and would also lead to averting 32 745 deaths in the US.[31] Finally, Sander et al. (2009)[30] used a stochastic simulation model of pandemic influenza in the USA, aiming to evaluate the potential economic impact of 16 different mitigation interventions from a societal perspective. Conclusively, targeted antiviral prophylaxis was both the most cost-saving and effective intervention with a cost of $127 per capita (€118·73 €[2017]), with expanded antiviral prophylaxis leading to a total of 282 329 QALYs gained.

Stockpile strategy

The stockpile strategy was noted in three of the studies included in this review. Based on the findings stockpiling antiviral prophylaxis in the context of a pandemic is both cost-saving for the society, and averts loss of life compared to no intervention – in total 258 342 were the total QALY's gained.[30] Moreover, pre-pandemic stockpiling of antiviral drugs could be more effective and cost-saving than no intervention if antiviral drugs were administered either solely as a treatment or as short-term prophylaxis for exposed individuals.[32] Finally, stockpiling was also found more effective than a no intervention scenario (averting 29 761 deaths in the US), although when compared with other interventions, expanded vaccination and prophylaxis were found to be more effective.[31]

Non-Pharmaceutical measures

Pre hospitalisation screening

Lankelma et al. (2019)[23], assessed the cost-effectiveness of screening patients with acute respiratory tract infection for influenza before hospital admission. Overall costs of screening were estimated at 98 968€[2017] for 1 546 tests and 624 cases and reported net savings of 388 317€[2017] for the healthcare system. Point-of-care testing for influenza before hospital admission was identified as a cost-effective intervention.[23]

Community contact reduction

Community contact reduction was noted in two studies, where it was either implemented solely or in combination with other pharmaceutical and non-pharmaceutical measures. Home confinement was noted as cost-effectiveness as a preventive measure in the context of influenza epidemics, if the proportion of compliance is adequate and infected individuals ask for medical assistance, regardless of the pandemic severity level.[26] Isolation of infected individuals was found to be among the most effective interventions, whereas combined with community contact reduction, personal protective measures and antiviral treatment, self-isolation had the lowest cost.[27]

School closure

The effectiveness and the economic burden of school closure were evaluated in four studies, highlighting that the duration of school closure and potentially combined strategies significantly affect its impact.

Sadique et al. (2008)[24] estimated the economic burden of school closure in the UK from a societal perspective, and showed that the estimated costs of school closure were high, at 0·28 - 1·68 billion, €[2017] per week and the authors concluded that school closure was likely to significantly add an extra economic burden on the health system through staff absenteeism, even if it delays the infectious disease's spreading.[24] Similarly, Sander et al. (2009)[31], who studied school closure as an additional intervention along with full targeted antiviral prophylaxis or prevaccination found that while it further improves health outcomes (gaining 51 QALYs), it was the least cost-effective measure as it increased the total cost to society by $2 700 per capita (€2 524 €[2017]). Additionally, school closure produced only a small reduction in illness attack rate, whether implemented in combination with other interventions or alone.[27] Finally, exclusive school closure for two weeks along with the continuous 50% workplace closure, antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis, had the lowest illness attack rate (2·4%) and one of the lowest costs. On the contrary, school closure as a sole intervention was not cost-effective.[28]

Personal protective measures

Personal protective measures such as face masks and hand hygiene were met in two of the included studies, noting that they could contribute to the control of a pandemic, depending, however, on the exposed and susceptible individuals' compliance rate, the setting and the overall burden of the pandemic.[27,29] Tracht et al. (2012)[29] aimed to assess the cost-effectiveness of facemasks (N95 grade) in reducing the spread of pandemic (H1N1) 2009, using a simulation model of the US population and identified an economic burden of 728·28 billion €[2017] (incl. direct and indirect costs). Notably, if masks are worn by 10% and 50% of the adult population of the US net savings were calculated at 418·75 billion €[2017]and 501·9 billion €[2017] respectively. Hence, the use of face masks could be a cost-effective preventive measure depending on the population's level of compliance.

DISCUSSION

The aim of this systematic literature review of econometric analysis studies was to assess the economics of preparedness when contrasted with the cost of infectious respiratory disease outbreaks in the European and OECD countries. Overall, the economic burden of infectious disease outbreaks are costly to healthcare systems, or to governments and society reflecting the medical costs for response activities including both the treatment of the confirmed cases and the surveillance and elimination of the disease's transmission, as well as indirect costs which where data was available were also substantial.

In general, the majority of direct costs seemed to mainly reflect the additional personnel hours, which were mandatory for the management of the infected cases, for the organisation of response planning and coordination, for the investigation of infected and susceptible cases, for providing educational training and materials, laboratory costs, as well as providing public information. With regards to indirect costs, they were estimated only in a few studies, which noted that indirect costs could in many cases be greater than the direct ones, especially when schooling or work is impacted across a population, such as loss of productivity significantly increased the economic burden. Moreover, our assessment noted that while all the pharmaceutical and non-pharmaceutical interventions lead to a health benefit for the individual or the society, the cost benefit of such interventions differed.

With regards to the potential non-pharmaceutical strategies, we identified that the use of personal protective measures, such as a mask, is both cost-saving and effective, similarly to pre-hospitalization screening among suspect cases which were also cost-saving and effective. On the other hand, all studies that assessed the impact of school closure noted that although it is an effective measure in reducing transmission, it is not cost-saving as it leads to increased economic burden. Moreover, when school closure was used as a sole intervention, then the use of limited duration school closure was significantly more cost-effective compared to continuous school closure.[28] Community contact reduction was identified to have a definite effective health impact but had ambiguous results with regards to its potential cost saving as one study[27] noted that it is a cost-saving intervention, while the other[24] noted that social distancing strategies, such as reduced workplace attendance, were not a cost-saving measure primarily due to productivity losses – especially during longer periods of closure. Productivity losses primarily were noted to arise from pandemic related deaths and illness coupled with those losses due to interventions such as workplace closure and child-care of an ill child, that would reduce overall productivity.[28] It is important to note that non-pharmaceutical strategies were mostly applied complementary to a pharmaceutical measure or in combination with other non-pharmaceutical strategies in order to enhance their effectiveness. However, their cost-effectiveness highly depended on the duration, the level of compliance from the population and the type and burden of the infectious disease.

With regards to pharmaceutical interventions, vaccination as a rapid response measure for infected and suspected individuals for was noted to have a more significant clinical effect than comparators and was more cost-saving in most cases. As for antiviral treatment, the majority of the findings noted that it is a cost-effective strategy, especially when combined with other pharmaceutical and non-pharmaceutical interventions or when used as targeted prophylaxis for exposed individuals. It is notable that targeted antiviral prophylaxis was the most cost-saving and effective intervention, while stockpiling was cost saving in most cases and averted loss of life when compared to no intervention.

The current number of economic evaluation or cost-effectiveness studies of influenza outbreak preparedness measures is small, with an increase shown since the 2009 influenza pandemic. There are only a limited number of related reviews, however of different scope focusing primarily on policy recommendations[34] or used dynamic transmission models in the included economic assessments of pandemic influenza preparedness measures based on significantly older studies.[35] Additionally, most of the existing review studies either evaluate the overall economic burden of the disease or the cost-effectiveness of different pharmaceutical and non-pharmaceutical interventions without necessarily them reflecting the economics of outbreaks of infectious respiratory diseases.

Placing the above into context and following the assessment of the methodological approaches used across studies it is essential to note what are the minimum contents that economic outbreaks of respiratory studies should include that would help inform future and upcoming work, especially in light of the COVID-19 pandemic. These include the clear noting of the study year, the population at risk and population infected, the type of economic perspective (i.e. healthcare, societal etc.), timeframe and discounting as also detailed reported direct and indirect costs of the respiratory outcome and the interventions were applied.

Strengths and limitations

A significant strength of this review is the comprehensive approach that was followed and the assessment of data quality -which indicated that the majority of the studies included were of high quality. Secondly, the synthesis of the results was performed using the DRM approach, which allowed for a direct comparison of the cost-effectiveness of each intervention to the null intervention.

However, there are a few limitations, firstly, costs and resources varied between different countries, different regional settings, and over time, making the cost component comparison of cost-effectiveness measures complex to interpret. Moreover, we only focused on EU and OECD analogous countries excluding Japan and South Korea, and hence our cost-effectiveness analyses are not applicable to other countries or middle- and low-income countries. Additionally, discrepancies in context and populations likely affect the implementation and efficacy of interventions, undermining even the effectiveness elements comparability in the cost-effectiveness measures, especially in complex multi-component public health interventions. Furthermore, this study was performed before the impact of COVID-19 and hence reflects the published knowledge before the current pandemic.

CONCLUSION

The value of this systematic review of econometric studies is to provide a synthesis of the evidence of the cost of respiratory infectious disease outbreaks and the cost-effectiveness of specific interventions that can be applied in response. Furthermore, our assessment identified a minimum number of econometric measures which should be recorded during respiratory infectious disease outbreaks that would aid future decision making. Our cost analysis results give evidence to public health policymakers as to the cost-effectiveness of a range of pharmaceutical and non-pharmaceutical intervention strategies which may be applied to mitigate or respond to infectious respiratory disease outbreaks.

ACKNOWLEDGEMENTS

We would like to thank Ioanna Lagou and Chrysa Chatzopoulou for contributing to data management.

CONTRIBUTORS

CV, JLB, ST and JS designed the study. KN and KZ undertook the literature review and extracted the data with help from JLB and RP. JLB and RP developed the search code. KZ, KN and KA analysed and interpreted the econometrics data. All authors participated in data evaluation and interpretation. CV and KN wrote the first draft of the manuscript with input from all authors. All authors reviewed and revised subsequent drafts.

Declaration of interests

We declare no competing interests.

Funding

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), to the PREP-EU Consortium, coordinated by Dr. Vardavas under specific contract No. 1 ECD.9630 within Framework contract ECDC/2019/001. The information and views in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Commission/Agency. The Commission/Agency do not guarantee the accuracy of the data included in this study. Neither the Commission/Agency nor any person acting on the Commission's/Agency's behalf may be held responsible for the use which may be made of the information contained therein.

Data sharing statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Patient and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

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TABLES

Table 1. Characteristics of cost of illness studies of influenza outbreaks, expressed in Euros (base year 2017)

Study, (Publication Year)	Setting, year	Perspective	Direct Costs (€, 2017)	Indirect Costs (€, 2017)
Prager et al. (2017)[18]	USA, n/a	Healthcare system, Governmental, Societal	**Seasonal (no vaccination)**: €5.92 billion **Seasonal (vaccination)**: €9.96 billion **Pandemic (no vaccination)**: €81.18 billion **Pandemic (vaccination)**: €65.59 billion	**Illness-related workdays losses** **a) Vaccination and no vaccination in a seasonal scenario:** Vaccination contributes to more workday losses than no vaccination **b) Vaccination and no vaccination in a pandemic scenario**: Vaccination reduces workday losses by 22.2 million days compared to no vaccination
Morales-Suárez-Varela et al. (2016)[17]	Spain, 2009-2010	Healthcare system , Societal	**Total direct cost/patient** Non-pregnant women: €3 908.70 Pregnant women: €2 227.10	**Total indirect cost/patient** Non-pregnant women: €107.18 Pregnant women: €63.83
Silva et al. (2014)[20]	France, 2010-2011	Payer, Societal	**Mean direct cost/patient** All ages – €53.43 0-4 yo – €73.91 5-14 yo – €52.79 15-65 yo – €35.26 ≥65 yo – €44.13 **Total direct costs** All ages – €107 883 835 0-4 yo – €18 908 254 5-14 yo – €52 474 781 15-65 yo – €21 590 741 ≥65 yo – €6 940 836	**Mean daily allowance cost due to work leave/patient** All ages – €22.38 0-4 yo – €0 5-14 yo – €0 15-65 yo – €97.88 ≥65 yo – €0
Higgins et al. (2011)[19]	Australia and New Zealand, 2009	Healthcare system	**Total mean cost**: €19,296,136 Total ICU costs: €6 107 069 Total non-ICU costs: €12 961 942 Mean cost of ICU/patient: €61 368 Mean cost of non-ICU/patient: €10 755 **Mean cost in ICU/per patient and per day**: €4 767	Non-reported
Wilson et al. (2009)[22]	New Zealand, 2009	Healthcare system	**Total ICU costs:** €40 807 660 Median ICU cost/patient: €22 540 Mean ICU cost/patient: €32 168,	Non-reported

			Total hospital costs/patient Median hospital cost: €39 696 Mean hospital cost: 53 553 **Treatment costs in ICU per sub-group** a) Cost/patient with and without pre-existing comorbidity €16 100 and €28 980, respectively b) Cost/patient with viral pneumonitis and with other influenza syndromes €22 212 and €12 880, respectively	
Rodríguez-Rieiro et al. (2009)[21]	Spain, 2009	Healthcare system	**Total cost**: €36 700 000 Median cost per hospitalization (concomitant chronic disease) €2 205 Median cost per hospitalization (without a medical condition) €1 172	Non-reported

ICU: intensive care unit, USA: United States of America

1: Confirmed or extrapolated/hypothetical cases on which they base the economic evaluation
*The adjustment was performed from Canadian $, United States $, Australian $, British pounds £ and converted to Euro (Germany has been selected as target currency in these cases) Currencies from European Union countries adjusted to their currency.
*The cost data include all forms of cost derived from inclusion studies, such as overall/total cost, mean/average cost, income loss, labour cost, household cost, savings, cost per case e.t.c.
*For studies without currency year indicated, the previous year of publication was selected for adjustment.

Table 2. Characteristics of full economic evaluation studies on preparedness and response measures of influenza outbreaks, expressed in Euros (base year 2017)

Study, (Publication year)	**Setting, Year**	**Population (n)**	**Interventions**	**Comparator**	**Economic evaluation outcomes**
Non-Pharmaceutical studies					
Lankelma et al. (2019)[23]	Netherlands, 2017-2018	Patients with acute RTI at the emergency department (1546 tests, 624 cases)	Point-of-care-testing for Influenza before hospital admission	2016-2017 influenza season	**Net Savings** €388 317 (after subtraction with costs) More than 80% of the total savings are due to the shorter length of stay and decreased hospital admissions. **The overall cost of intervention:** €98 968 Laboratory costs at €72 202 Clinical aspects costs at €26 767
Orset (2018)[26]	France, 2014	200 participants, data extrapolated	7-day home confinement	No intervention	**Costs associated with home confinement** **a) Direct costs** For adults: €742/case For elderly: €1 191/case **b) Indirect costs** **Productivity losses/case** For adults: €550. For elderly: €125 **Costs of death/case** The cost of death for children is estimated at €22-128, for adults at €63-361 and for elderly at €2 667-15 389 **Loss of productivity due to influenza/case** Productivity loss in case of adult sickness: €88.70 (incl. absent from work + reduced productivity) Productivity loss in case of a sick child for the adult (mainly mother): €97.62
Sadique et al. (2008)[24]	UK, 2005	Working parents with depending children	School closure	No intervention	**Cost of school closure:** Between €280 million - €2.8 billion/week **Cost of absenteeism:** €1.4 billion Adjusting for informal care, the cost reduced between €552 - €635 million per week. Adjusting for the elasticity of production the cost reduced to €970 327 320- €1.1 billion per week
Tracht et al. (2012)[29]	USA, (2009-2010 influenza	Simulation of the US (302 million	Population use of face masks (N95) on the spread of a pandemic	No intervention	**Net savings** If masks are worn by 10% of the adult population: €418.75 billion If masks are worn by 50% of the adult population: €501.9 billion

	season)	people:73 million children, 191 million adults, and 38 million seniors)			**Economic burden, if no intervention**: €728.28 billion (incl. direct and indirect costs)
Combined Pharmaceutical and non-Pharmaceutical strategies					
Saunders-Hastings et al. (2017)[27]	Canada, n/a	A simulation of Ottawa, Canada (1.2 million)	**1.**Vaccination + antiviral treatment **2.**Vaccination + antiviral treatment + antiviral prophylaxis **3.** Community contact reduction + personal protective measures + isolation **4.** Community-contact reduction + personal protective measures + isolation + antiviral treatment **5.** School closure + community contact reduction + personal protective measures + quarantine **6.** All interventions	No intervention	**Cost/life-year saved (LYG) Vs no intervention** **1.**€1 700/LYG **2.**€1 769/LYG **3.**€4 394/LYG **4.** €4 447/LYG **5.** €171 590/LYG **6.**€131 679/LYG **Total economic burden** For all scenarios, the economic burden ranges between €75 758 to €1 416 351
Halder et al. (2011)[28]	Australia, 2009	A community in Western Australia (30,000)	Different combinations of durations of individual school closure, antiviral treatment, household antiviral prophylaxis, extended antiviral prophylaxis, 50 % workplace closure, 50% community contact reduction	No intervention	**Cost/case averted:** Antiviral drug strategies + 2 weeks school closure: €396 per case averted (cost-effective) Short-duration school closure: €820/case averted ISC, continuously + 50% workplace. continuously: €6 204/case averted In case of 2 weeks for the above combination: €1 891/case averted ISC, continuously: €2 180/case averted **Total cost, per 100.000 population** The dual strategy of individual school closure for two weeks (ISC) along with the 50% community contact reduction (CCR): €3.39 million The dual strategy of continuous individual school closure (ISC) along with the continuous – 50% workplace closure (WP): €61.3 million. **Productivity loss due to illness and interventions per 100 000 population** ISC (cont.) + WP (cont.): €90.21 million Combined antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis: €4.63
Yarmand et al. (2010)[30]	USA, (2009-2010 influenza	North Carolina State University	Vaccination	Self-Isolation	**High levels of interventions** Self-isolation is incrementally cost-effective than vaccination This has been presented for most of cost ratio values.

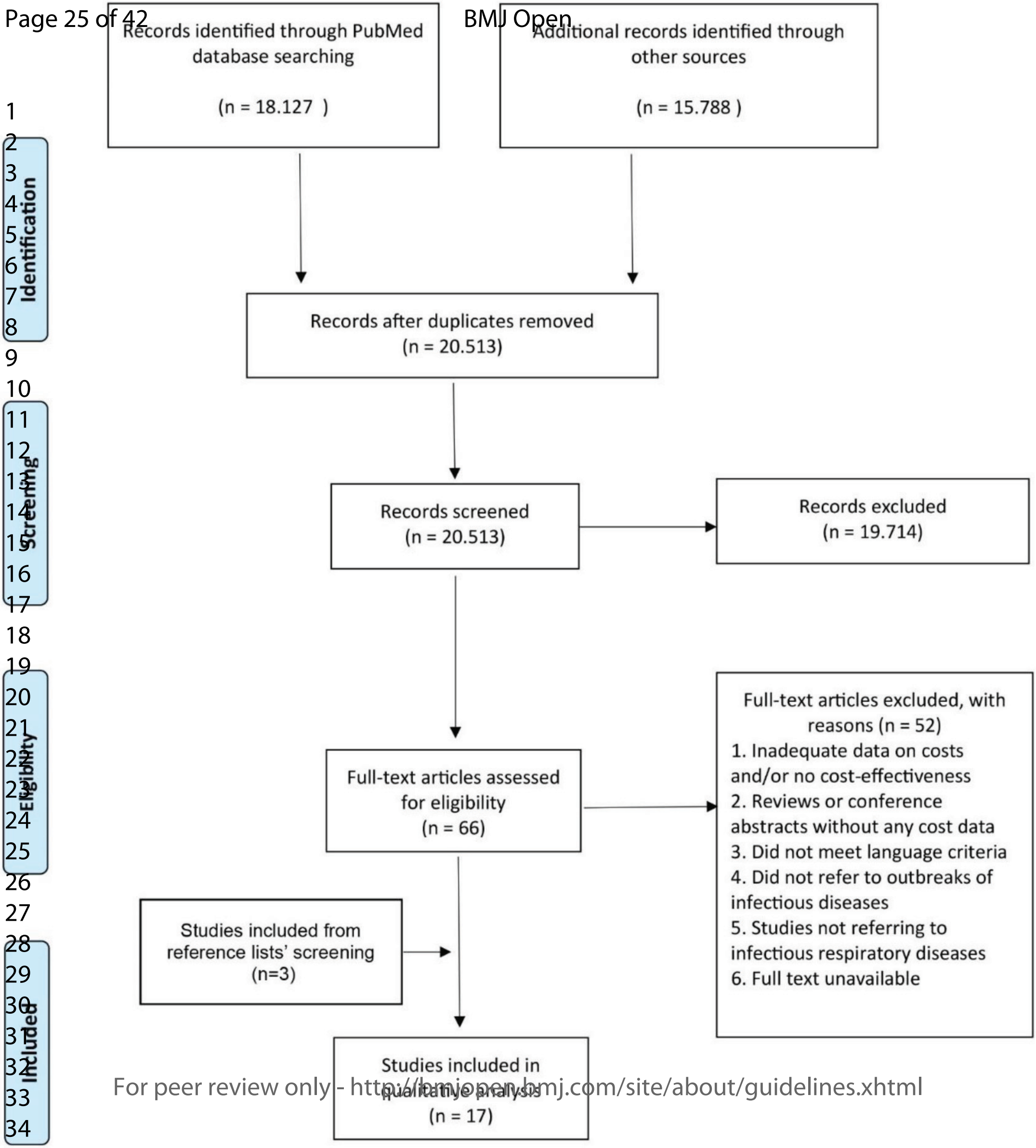
	season)	undergraduate students (23,087)			**Low levels of interventions** Vaccination is incrementally cost-effective than self-isolation The results were robust, even in sensitivity analyses.
Sander et al. (2009)[31]	USA, n/a	Residents of a 1.632-million-person city	**1.** HTAP25 with a stockpile for 25% of the population **2.** HTAP50 with a stockpile for 50% of the population **3.** HTAP with an unlimited stockpile **4.** School closure for 26 weeks **5.** Prevaccination 70% of the population with a low efficacy vaccine **6.** HTAP25 + school closure: **7.** HTAP50 + school closure: **8.** HTAP + school closure: **9.** Prevaccination + school closure: Prevaccinating 70% population with the low-efficacy vaccine, plus closing all schools for 26 weeks **10.** Treatment only: Treating all cases with antivirals **11.** FTAP25 for household contacts and 60% of work/school contacts, stockpile for 25% of the population **12.** FTAP50 for household contacts and 60% of work/school contacts, stockpile for 50% of population **13.** FTAP for household contacts and 60% of work/school contacts, stockpile unlimited **14.** FTAP25 + school closure **15.** FTAP50 + school closure **16.** FTAP + school closure	No intervention	**Cost/capita and cost-effectiveness outcomes** **1**.FTAP is cost-effective (54% reduction attack rate, €119 per capita) **2.** Prevaccination (48% reduction attack rate, €131 per capita) **3.** School closure in combination with each of the above is the least cost-effective (€2 524 per capita) ICUR of FTAP: €42 959 ICUR of prevaccination and school closure: €43 106 **Cost-saving** FTAP and prepandemic vaccination are cost-saving compared to no intervention
Pharmaceutical only strategies					
Khazeni et al. (2009)[32]	USA, n/a	A U.S. metropolitan city (8.3 million)	**1.** Stockpiled strategy **2.** Expanded adjuvanted vaccination **3.** Expanded antiviral prophylaxis	No intervention	**Intervention and treatment costs** 1. Stockpiled strategy: Total cost of €30.1 million and contribution to €288 million treatment costs 2. Expanded adjuvanted vaccination: Total cost of €179 million and contribution to €166 million treatment costs 3. Expanded antiviral prophylaxis: Total cost of €58.4 million and contribution to €266 million treatment costs

					4. No intervention: contribution to €462 million treatment costs **Cost/QALY gained** 1. Stockpiled strategy compared to no intervention: €7 894/QALY 2. Expanded adjuvanted vaccination (at 80% effectiveness) relative to stockpiled strategy: €8 600/QALY 3. Expanded antiviral prophylaxis has a less favourable cost-effectiveness ratio than adjuvanted vaccination Expanded adjuvanted vaccination shown to be a cost-effective intervention because it contributes to 404 030 QALYs at $10 844 per QALY gained relative to stockpiled strategy.
Balicer et al. (2005)[33]	Israel, n/a	Population of Israel (1,618,200 cases/patients)	**Stockpiling with antiviral drugs** **1.**Therapeutic use (all patients) **2.**Therapeutic use (high-risk patients) **3.** Preexposure Long-term prophylaxis (all population) **4.** Preexposure Long-term prophylaxis (high-risk population) **5.** Short-term postexposure prophylaxis for all close contacts	No intervention	**Cost-benefit ratio (CBA)** Therapeutic use (incl. all and high-risk patients): 2.44-3.68 Preexposure (incl. entire and high-risk population): 0.37-0.38 Postexposure: 2.49 Stockpiling with antiviral drugs for high-risk patients remain cost-saving strategy even if the annual probability of a pandemic remains >1 every 80 years. **Overall cost** The overall health-related costs: €56 234 057 The overall cost to the economy: €535 245 986 **Workdays lost due to illness** 6 536 240 or 4 days/patient
Medema et al. (2004)[25]	n/a,	Developed Countries (1 Billion people)	**1.**Egg-based vaccines with 17% population coverage **2.**Cell culture-based vaccines with 37% population coverage	No intervention	**Cost per life-year gained** In general, vaccination is cost-effective. Cell culture-based vaccines: €3 376/LYG (cost-effective) **Cost per intervention** Egg-based: €2.6 billion Cell culture-based: €5.87 billion **Net savings** Egg-based: €8.5 billion Cell culture-based: €5.87 billion Savings: €1.84 billion

CBA: Cost-benefit ratio, LYG: Life-year gained, VSL: Value of statistical life, FTAP: Full targeted antiviral prophylaxis, ISC: Individual school closure, WP: Workplace closure, CCR: Community contact reduction, ICER: Incremental cost-effectiveness ratio, ICUR: Incremental cost-utility ratio; HTAP: Household targeted antiviral prophylaxis

Figure 1. Flowchart

Figure 2. Dominance Ranking Matrix for Pharmaceutical and non-pharmaceutical strategies


Identification
Screening
Eligibility
Included
Records identified through PubMed database searching
(n = 18.127)
Additional records identified through other sources
(n = 15.788)
Records after duplicates removed
(n = 20.513)
Records screened
(n = 20.513)
Records excluded
(n = 19.714)
Full-text articles assessed for eligibility
(n = 66)
Full-text articles excluded, with reasons (n = 52)
1. Inadequate data on costs and/or no cost-effectiveness
2. Reviews or conference abstracts without any cost data
3. Did not meet language criteria
4. Did not refer to outbreaks of infectious diseases
5. Studies not referring to infectious respiratory diseases
6. Full text unavailable
Studies included from reference lists' screening
(n=3)
Studies included in qualitative analysis
(n = 17)

Type of Intervention	Costs*	Health benefit**
Pharmaceutical strategies		
Vaccination as a response measure		
Sander et al. (2009)	–	+
Khazeni et al. (2009)	0	+
Madema et al. (2004)	–	+
Saunders-Hastings et al. (2017)	–	+
General vaccination		
Sander et al. (2009)	–	+
Antiviral drugs		
Sander et al. (2009)	–	+
Halder et al. (2011)	–	+
Balicer et al. (2005)	–	+
Saunders-Hastings et al. (2017)	–	+
Khazeni et al. (2009)	0	+
Stockpile strategy		
Sander et al. (2009)	–	+
Balicer et al. (2005)	–	+
Khazeni et al. (2009)	0	+
Non-Pharmaceutical strategies		
Volunteer isolation		
Orset (2018)	–	+
Saunders-Hastings et al. (2017)	–	+
Pre hospitalisation screening		
Lankelma et al., (2019)	–	+
Community contact reduction		
Saunders-Hastings et al. (2017)	–	+
Halder et al. (2011)	+	+
School closure		
Sadique et al. (2008)	+	+
Saunders-Hastings et al. (2017)	+	+
Halder et al. (2011)	+	+
Sander et al. (2009)	+	+
Personal protective measures		
Tracht et al. (2012)	–	+
Saunders-Hastings et al. (2017)	–	+

**+: the intervention is less cost saving than the comparator; 0: the intervention is equally cost saving with the comparator; -: the intervention is more cost saving than the comparator*

***the intervention is more effective than the comparator; 0: the intervention is equally effective with the comparator; -: the intervention is leff effective than the comparator*

Appendix

Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis: Supplementary Information

Appendix 1. Search concept construction

OVID MEDLINE

Date of Search	OVID Medline		
	#	Search Terms	Hits
29/7/2019	1	Economics/	27061
	2	"costs and cost analysis"/	47439
	3	Cost allocation/	1997
	4	Cost-benefit analysis/	77184
	5	Cost control/	21373
	6	Cost savings/	11287
	7	Cost of illness/	25397
	8	Cost sharing/	2443
	9	"deductibles and coinsurance"/	1716
	10	Medical savings accounts/	529
	11	Health care costs/	37249
	12	Direct service costs/	1171
	13	Drug costs/	15395
	14	Employer health costs/	1088
	15	Hospital costs/	10427
	16	Health expenditures/	18983
	17	Capital expenditures/	1987
	18	Value of life/	5653
	19	exp economics, hospital/	23708
	20	exp economics, medical/	14108
	21	Economics, nursing/	3989
	22	Economics, pharmaceutical/	2874
	23	exp "fees and charges"/	29802
	24	(low adj cost).mp.	51166
	25	(high adj cost).mp.	13286
	26	(health?care adj cost$).mp.	10352
	27	(fiscal or funding or financial or finance).tw.	136748
	28	(cost adj estimate$).mp.	2132
	29	(cost adj variable).mp.	42
	30	(unit adj cost$).mp.	2368
	31	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	277405
	32	Economic evaluation.mp.	9144
	33	(Cost?effectiveness analysis or CEA).mp.	21933
	34	(Cost?utility analysis or CUA).mp.	1153
	35	(Cost?benefit analysis or CBA).mp.	26471
	36	(Cost?consequence analysis or CCA).mp.	7687
	37	(Cost?minimi?sation analysis or CMA).mp.	3583
	38	(cost?outcome or marginal analysis).mp.	204
	39	exp Cost benefit analysis/ or exp budgets/	90077
	40	investment$.mp. or investments/	39609
	41	or/1-40	769608
	42	exp Emergency Preparedness/	2678
	43	exp Preparedness, Emergency/	2678
	44	(Community Preparedness or Community Recovery or Emergency Operations Coordination or (Emergency Public Information and Warning) or Fatality Management or Information Sharing or Mass Care or Medical Countermeasure Dispensing or (Medical Materiel Management and Distribution)	2614

		or Medical Surge or Non-Pharmaceutical Interventions or Public Health Laboratory Testing).mp.	
	45	exp Public Health Surveillance/	2623
	46	(Epidemiological Investigation or (Responder Safety adj Health) or Volunteer Management).mp.	2867
	47	(disaster preparedness or public health emergencies).mp.	2012
	48	((Detection adj assessment) or policy development or policy implementation or policy adaptation or health services or (coordination adj communication) or emergency risk communication or personal preparedness).mp.	393599
	49	((state or local or national or legal or business or healthcare) and preparedness).mp.	4359
	50	(vaccination or immuni?ation or anti?viral medication or personal hygiene or hand hygiene or household ventilation or ((food and safety) or storage) or food hygiene or respiratory etiquette or (washing and saniti?ing) or social distancing or triage or food security or (emergency adj3 food) or (school adj3 closure) or public gathering* or public meeting* or household isolation or quarantine or PPE or personal protective equipment or (environmental adj3 cleaning)).mp.	545475
	51	or/42-50	940853
	52	exp disease outbreak/ or exp communicable diseases/	119498
	53	(disease outbreak or outbreak or epidemic or pandemic or public health emergency).mp.	150101
	54	(avian flu or abola or EVD or H1N1 or H5N1 or infectious disease or influenza or swine flu or flu or MERS or Middle East Respiratory Syndrome).mp.	165207
	55	(SARS or Severe Acute Respiratory syndrome or measles or zika or cholera or H7N9 or dengue or fever or plague or fever or malaria or polio).mp.	381260
	56	(Bacillus cereus or Campylobacter jejuni or Clostridium or Cryptosporidium or Cyclospora cayetanensis or (E adj coli) or Hepatitis A or Listeria monocytogenes or Noroviruses or Salmonella or Shigella or Staphylococcus aureus or Staphylococcus or Vibrio parahaemolyticus or Vibrio vulnificus).mp.	493801
	57	(Diphtheria or Haemophilus influenzae type b or Hib or Hepatitis B or Human Papillomavirus or HPV).mp.	165778
	58	((Meningococcal adj Infection$) or Mump$ or Pertussis or Whooping Cough or Pneumococcal Infection$ or Polio or Rotavirus or Rubella or German Measles or Tetanus or varicella or chicken pox or vectorbourne diseases or vector?bourne disease$ or waterbourne diseases or water?bourne disease$ or Cholera or Diarrhea or diarrhoea).mp.	255768
	59	(Typhoid fever or Giardiasis or Schistosomiasis or Dracunculiasis or Dysentery or Cryptosporidiosis or amoebiasis or Traveler$s diarrhea or travelers diarrhoea).mp.	68954
	60	exp infectious disease medicine/ or exp malaria/ or exp influenza, human/ or SARS virus/ or exp norovirus/ or exp coronavirus infections/ or exp measles/ or exp poliomyelitis/ or exp chickenpox/	165698
	61	(anthrax or botulism or brucellosis or campylobacter enteritis or chikungunya or chlamydia$ or CJD or Creutzfeldt?Jakob).mp.	63613
	62	(diptheria or echinococcosis or gonococcal or haemophilus influenzae or hepatitis or HIV or AIDS or human immunodeficiency virus or acquired immunodeficiency syndrome).mp.	714394
	63	(legionnaires?disease or leptospirosis or listeriosis or lyme or streptococcus pneumoniae or Q fever or rabies or congenital rubella or salmonella or shiga toxin or verocytotoxin?producing E?coli or STEC or VTEC or HUS or haemoltic?uraemic or hemoltic?uremic).mp.	182938
	64	(shigellosis or smallpox or syphilis or congenital syphilis or tick?borne viral encephalitis or congenital toxoplasmosis or	341238

		trichinellosis or tuberculosis or TB or typhoid or paratyphoid or VHF or viral hemorrhagic fever$ or viral haemorrhagic fever$ or West Nile virus or Yellow fever or (enteritis adj3 yersinia)).mp.	
	65	or/52-64	2357602
	66	41 and 51 and 65 (studies before 2003 excluded)	18127

EMBASE

Date of Search	EMBASE		
	#	Search Terms	Hits
29/7/2019	1	Socioeconomics/	133589
	2	Cost benefit analysis/	81690
	3	Cost effectiveness analysis/	143890
	4	Cost of illness/	18428
	5	Cost control/	65812
	6	Economic aspect/	110246
	7	Financial management/	110636
	8	Health care cost/	181209
	9	Health care financing/	13089
	10	Health economics/	32080
	11	Hospital cost/	20343
	12	(fiscal or financial or finance or funding).tw.	178545
	13	Cost minimization analysis/	3375
	14	(cost adj estimate$).mp.	3181
	15	(cost adj variables$).mp.	188
	16	(unit adj cost$).mp.	4210
	17	investment$.mp. or investments/	49607
	18	or/1-17	906830
	19	"Emergency Preparedness".tw.	1780
	20	(Community Preparedness or Community Recovery or Emergency Operations Coordination or (Emergency Public Information and Warning) or Fatality Management or Information Sharing or Mass Care or Medical Countermeasure Dispensing or (Medical Materiel Management and Distribution) or Medical Surge or Non-Pharmaceutical Interventions or Public Health Laboratory Testing).mp.	3358
	21	exp Public Health Surveillance/	210835
	22	(Epidemiological Investigation or (Responder Safety adj Health) or Volunteer Management).mp.	3638
	23	(disaster preparedness or public health emergencies).mp.	2176
	24	((Detection adj assessment) or policy development or policy implementation or policy adaptation or health services or (coordination adj communication) or emergency risk communication or personal preparedness).mp.	124325
	25	((state or local or national or legal or business or healthcare) and preparedness).mp.	5302
	26	(vaccination or immuni?ation or anti?viral medication or personal hygiene or hand hygiene or household ventilation or ((food and safety) or storage) or food hygiene or respiratory etiquette or (washing and saniti?ing) or social distancing or triage or food security or (emergency adj3 food) or (school adj3 closure) or public gathering* or public meeting* or household isolation or quarantine or PPE or personal protective equipment or (environmental adj3 cleaning)).mp.	703894
	27	or/19-26	1031364

	28	exp disease outbreak/ or exp communicable diseases/	119087
	29	(disease outbreak or outbreak or epidemic or pandemic or public health emergency).mp.	207717
	30	(avian flu or abola or EVD or H1N1 or H5N1 or infectious disease or influenza or swine flu or flu or MERS or Middle East Respiratory Syndrome).mp.	198862
	31	(SARS or Severe Acute Respiratory syndrome or measles or zika or cholera or H7N9 or dengue or fever or plague or fever or malaria or polio).mp.	561066
	32	(Bacillus cereus or Campylobacter jejuni or Clostridium or Cryptosporidium or Cyclospora cayetanensis or (E adj coli) or Hepatitis A or Listeria monocytogenes or Noroviruses or Salmonella or Shigella or Staphylococcus aureus or Staphylococcus or Vibrio parahaemolyticus or Vibrio vulnificus).mp.	579612
	33	(Diphtheria or Haemophilus influenzae type b or Hib or Hepatitis B or Human Papillomavirus or HPV).mp.	241684
	34	((Meningococcal adj Infection$) or Mump$ or Pertussis or Whooping Cough or Pneumococcal Infection$ or Polio or Rotavirus or Rubella or German Measles or Tetanus or varicella or chicken pox or vectorbourne diseases or vector?bourne disease$ or waterbourne diseases or water?bourne disease$ or Cholera or Diarrhea or diarrhoea).mp.	421975
	35	(Typhoid fever or Giardiasis or Schistosomiasis or Dracunculiasis or Dysentery or Cryptosporidiosis or amoebiasis or Traveler$s diarrhea or travelers diarrhoea).mp.	56723
	36	exp infectious disease medicine/ or exp malaria/ or exp influenza, human/ or SARS virus/ or exp norovirus/ or exp coronavirus infections/ or exp measles/ or exp poliomyelitis/ or exp chickenpox/	213621
	37	(anthrax or botulism or brucellosis or campylobacter enteritis or chikungunya or chlamydia$ or CJD or Creutzfeldt?Jakob).mp.	78479
	38	(diptheria or echinococcosis or gonococcal or haemophilus influenzae or hepatitis or HIV or AIDS or human immunodeficiency virus or acquired immunodeficiency syndrome).mp.	938033
	39	(legionnaires?disease or leptospirosis or listeriosis or lyme or streptococcus pneumoniae or Q fever or rabies or congenital rubella or salmonella or shiga toxin or verocytotoxin?producing E?coli or STEC or VTEC or HUS or haemoltic?uraemic or hemoltic?uremic).mp.	206207
	40	(shigellosis or smallpox or syphilis or congenital syphilis or tick?borne viral encephalitis or congenital toxoplasmosis or trichinellosis or tuberculosis or TB or typhoid or paratyphoid or VHF or viral hemorrhagic fever$ or viral haemorrhagic fever$ or West Nile virus or Yellow fever or (enteritis adj3 yersinia)).mp.	313309
	41	or/28-39	2651637
	42	18 and 27 and 41 (studies before 2003 excluded)	14223

ECONLIT

Date of Search	EconLit		
	#	Search Terms	Hits
30/8/2019	1	cost OR (deductibles and coinsurance) OR Medical savings accounts OR health expenditure OR economic OR (fees and charges) OR Economic evaluation OR cost effectiveness analysis OR Cost utility analysis OR cost benefit analysis OR Cost consequence analysis OR Investment	1,344,466
30/8/2019	2	(Emergency Preparedness) OR Preparedness OR emergency OR Surveillance OR disaster OR (detection or diagnosis or identification or early detection) OR screening OR vaccination OR hygiene OR school closure OR quarantine	48,619
30/8/2019	3	disease outbreak OR disease OR infectious diseases OR communicable diseases OR outbreak OR pandemic OR epidemic	9,194
31/8/2019	4	S1 AND S2 AND S3 (limitation: from 2003 to 2019)	965

IDEAS REPEC

Date of Search	IDEAS REPEC			
	Search Term 1	Search Term 2	Search Term 3	Results (n)
28/7/2019	cost-effective	infectious		139
28/7/2020	Emergency Public Information and Warning	cost		8
28/7/2021	Health Surveillance	infectious	cost	10
30/7/2022	economics	health preparedness		39
30/7/2023	cost-effectiveness	cost effectiveness	health preparedness	8
30/7/2024	prevention	cost	disease outbreaks	42
30/7/2025	economic evaluation	Public health surveillance		12
30/7/2026	investment	Infectious disease	outbreak	16
30/7/2027	economics	H1N1		16
30/7/2028	economics	flu	outbreak	25
1/8/2019	Cost-effectiveness	ebola		4
1/8/2019	economics	disease threats		171
1/8/2019	pandemic	economic	cost	42

Appendix 2. Total quality appraisal score (in percentages) for all included studies (n=17)

Appendix 3. Quality appraisal score by item/question for the partial economic evaluation studies (n=6)

Appendix 4. Quality appraisal by item/question of the full evaluation studies (n=11)

Appendix 5. Characteristics of cost analyses studies of influenza outbreaks

Study, (Publication Year)	Setting, year	Study population (n)	Economic Evaluation	Approach	Perspective	Time Horizon	Type of Sensitivity analysis
Prager et al. (2017)	USA, n/a	The population of the USA	Cost of illness (although mentions about cost-effective of vaccination in the pandemic scenario, No CEA outcomes)	Simulation model	Healthcare system, Governmental, Societal	Not clearly stated	Performed, unclear
Morales-Suárez-Varela et al. (2016)	Spain, 2009-2010	Unvaccinated women of childbearing age with influenza A (H1N1)	Partial Economic Evaluation (Cost of illness)	Observational	Healthcare system, Societal	4 months	Not performed
Silva et al. (2014)	France, 2010-2011	Population with Influenza B (201)	Partial Economic Evaluation (cost of illness)	Observational	Payer, Societal	3 months	One-way sensitivity analysis and probabilistic analysis
Higgins et al. (2011)	Australia and New Zealand, 2009	All Influenza cases (H1N1) in New Zealand and Australia (762)	Partial Economic Evaluation Cost of illness	Observational	Healthcare system	3 months	Not performed
Wilson et al. (2009)	New Zealand, 2009	All Influenza hospitalisations in New Zealand) 1224 – 1122 hospitalizations and + 122 ICU	Partial Economic Evaluation, Cost of illness (incl. hypothetical cost-effectiveness analysis)	Observational	Healthcare system	12 months	Probabilistic sensitivity analysis
Rodríguez-Rieiro et al. (2009)	Spain, 2009	All Spanish patients with H1N1 (11,449)	Partial Economic Evaluation (Cost of illness)	Observational	Healthcare system	12 months	Not performed

Appendix 6. Characteristics of studies on preparedness and response measures of influenza outbreaks

Study, (Publication year)	Setting, Year	Population (n)	Economic Evaluation Approach	Perspective	Timeframe	Discount	Sensitivity analysis
Observational studies							
Lankelma et al. (2019)	Netherlands, 2017-2018	Patients with acute RTI at the emergency department (1546 tests, 624 cases)	Partial Economic Evaluation	Healthcare system	4,5 months	N/A	Not performed
Sadique et al. (2008)	UK, 2005	Working parents with depending children	Partial Economic Evaluation	Societal	1 year	N/A	Scenarios
Simulation or mathematical models							
Orset (2018)	France, 2014	200 participants, data extrapolated	Both cost-benefit and cost-effectiveness analysis	Public health and societal	1 year	1% for costs	Not performed
Saunders-Hastings et al. (2017)	Canada, n/a	A simulation of Ottawa, Canada (1.2 million)	cost-effectiveness analysis	Healthcare system	Lifetime	1.5%	Multivariate sensitivity analyses
Halder et al. (2011)	Australia. 2009	A community in Western Australia (30,000)	cost-effectiveness analysis	Healthcare and Societal	Lifetime	3%	Scenarios
Tracht et al. (2012)	USA, (2009-2010 influenza season)	Simulation of the US (302 million people:73 million children, 191 million adults, and 38 million seniors)	cost-effectiveness analysis	Healthcare system and societal	1 year	N/A	Multivariate sensitivity analyses
Yarmand et al. (2010)	USA, (2009-2010 influenza season)	North Carolina State University undergraduate students (23,087)	cost-effectiveness analysis	Healthcare system	5 months	N/A	One-way and two-way sensitivity analyses
Sander et al. (2009)	USA, n/a	Residents of a 1 632-million-person city	Cost Utility Analysis	Societal	6 months	3%	Multivariate sensitivity analyses
Khazeni et al. (2009)	USA, n/a	A U.S. metropolitan city (8.3 million)	cost-effectiveness analysis	Societal	Lifetime	3% for benefits/ costs	Monte Carlo probabilistic sensitivity analysis
Balicer et al. (2005)	Israel, n/a	Population of Israel (1 618 200 cases)	Cost-benefit analysis	Healthcare system Societal	Lifetime	Not specified	Multivariate sensitivity analyses
Medema et al. (2004)	UK, Germany, Netherlands, (2004)	Developed Countries (1 Billion people)	Cost-effectiveness analysis	Healthcare system	Not clearly stated	5%	Performed unclear

RTI: Acute respiratory tract infection, N/A: Not applicable, UK: United Kingdom, US: United States

Appendix 7. Comparative analysis of health indexes when averting/responding to respiratory disease outbreaks

Study / year	Intervention(s)/Screening methods vs. comparators	Outcomes/benefits
Prager et al. 2016	Case 1: No Vaccination, Seasonal Outbreak Case 2: No Vaccination, Pandemic Outbreak Vs. Case 3: Vaccination, Seasonal Outbreak Case 4: Vaccination, Pandemic Outbreak	**Productivity loss and behavioural response** **In the case of a pandemic influenza outbreak** Vaccination: 1. Reduces illness-related workday losses from 83.3 million days to 61.1 million days (a reduction of 22.2 million days). 2. Causes 7.4 million days of workday losses due to the time that people spend on getting the vaccination doses. 3. Can reduce public avoidance behaviours by 25%. **In the case of a seasonal influenza outbreak** Vaccination: 1. Reduces illness-related workday losses from 18.7 million days to 13.9 million days (a reduction of 4.8 million days). 2. Causes 6.7 million days of workday losses due to the time that people spend obtaining vaccinations. 3. Can reduce public avoidance behaviours by 25%.
Medema et al. 2004	1. Egg-based vaccine manufacture 2. Cell culture-based vaccine manufacture Vs. No intervention	**Cases, PCP consultations and hospitalizations prevented** **Cell culture-based intervention vs no intervention:** Cell culture-based intervention avoids 75 million influenza cases, 3.78 million PCP consultations for influenza treatment and, respectively, 5.81 million and 1.21 million influenza-related hospitalizations and excess deaths. **Egg-based vaccine intervention vs no intervention:** Egg-based vaccine intervention leads to vaccination of 17% of the population, which avoids 29.8 million influenza cases, 1.74 million PCP visits, 2.67 million hospitalizations and 556 000 deaths **Cell culture-based intervention vs egg-based vaccine intervention with 17% vaccine coverage:** Cell culture-based intervention strategy leads to vaccination of 37% of the population, avoiding an additional 35 million influenza cases, 2.04 million PCP consultations for influenza treatment, 3.14 million influenza-related hospitalizations and 654 500 excess deaths **Years of life lost (YLL)** Cell culture-based intervention strategy: 2.56 million

Saunders-Hastings et al. 2017	1. Vaccination and antiviral treatment 2. Vaccination, antiviral treatment and antiviral prophylaxis 3. Community-contact reduction, personal protective measures and voluntary isolation 4. Community-contact reduction, personal protective measures, voluntary isolation and antiviral treatment 5. School closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine 6. All interventions Vs. 7. No intervention	**Hospitalizations** In case of no intervention, a total of 2 472 pandemic-associated hospitalizations have been estimated. Following no intervention, vaccination interventions (combined with other interventions) contributed to 765-815 hospitalizations. Last, school closure, combined with other interventions, contributed to 108-550 hospitalizations. **YLL** 1. 3,026 2. 2,801 3. 1,767 4. 1,607 5. 1,393 6. 267 7. 9,421 **Reductions of illness (H2N2 cases)** Vaccination, personal protective measures, combined voluntary isolation and quarantine procedures resulted in the greatest reductions, producing attack rates of 50.0%, 45.5% and 33.9%, respectively. Antiviral treatment, antiviral prophylaxis, school closure and community-contact reduction produced only small reductions in illness attack rate, whether implemented alone or in combination with other interventions. Even in the absence of any pharmaceutical intervention, adherence to rigorous non-pharmaceutical protocols -school closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine-resulted in a reduction of the illness attack rate to 15.2%,
Khazeni et al. 2009	1) Vaccination and antiviral pharmacotherapy in quantities similar to those currently available in the U.S. stockpile (stockpiled strategy), 2) Stockpiled strategy but with the expanded distribution of antiviral agents (expanded prophylaxis strategy), and 3) Stockpiled strategy but with the adjuvanted vaccine (expanded vaccination strategy). Vs. no intervention	**Clinical attack rate** The clinical attack rate has been 11%, 17%, 19% and 33% for expanded adjuvanted vaccination, expanded antiviral prophylaxis, Stockpiled strategy and for no intervention, respectively. **Deaths averted** Expanded adjuvanted vaccination – 45 941 deaths averted Expanded antiviral prophylaxis – 32 745 deaths averted Stockpiled strategy – 29 761 deaths averted No intervention - No deaths averted
Sander et al.	1. HTAP25 with a stockpile for 25% of the population 2. HTAP50 with a stockpile for 50% of the population 3. HTAP with an unlimited stockpile	**QALYs gained, total** Expanded adjuvanted vaccination – 404 030 total QALYs gained Expanded antiviral prophylaxis – 282 329 total QALYs gained

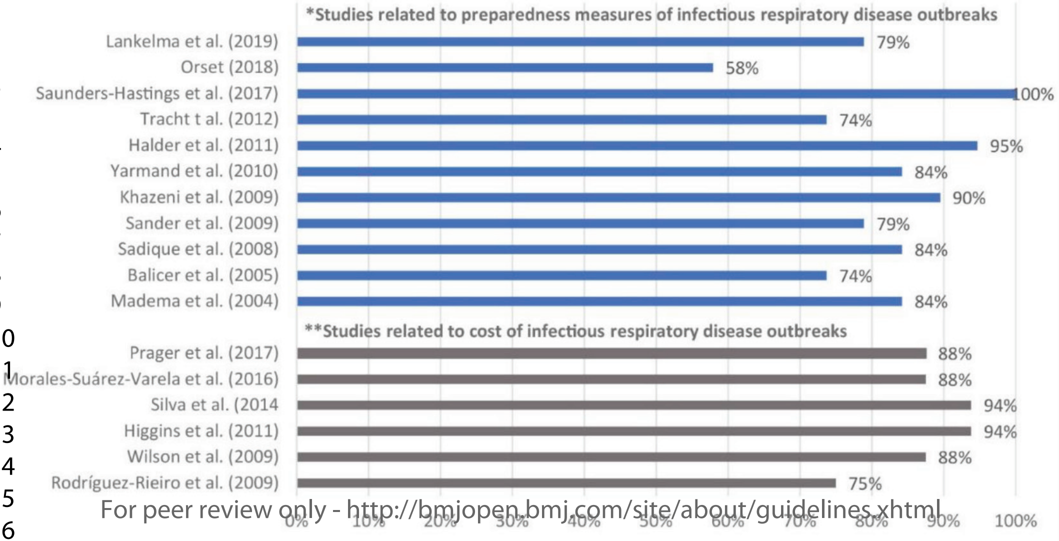
2009	4. School closure for 26 weeks 5. Prevaccination 70% of the population with a low efficacy vaccine 6. HTAP25 + school closure: 7. HTAP50 + school closure: 8. HTAP + school closure: 9. Prevaccination + school closure: Prevaccinating 70% population with the low-efficacy vaccine, plus closing all schools for 26 weeks 10. Treatment only: Treating all cases with antivirals 11. FTAP25 for household contacts and 60% of work/school contacts, stockpile for 25% of the population 11. FTAP50 for household contacts and 60% of work/school contacts, stockpile for 50% of population 12. FTAP for household contacts and 60% of work/school contacts, stockpile unlimited 14. FTAP25 + school closure 13. 15. FTAP50 + school closure 14. 16. FTAP + school closure	Stockpiled strategy – 258 342 total QALYs gained No intervention - No QALYs gained **QALYs per 1000 population, total** All interventions gained a similar amount of QALYs, with some differences between them (21,141 for no intervention to 21 403 for prevaccination and school closure). Compared to FTAP not involving school closure, FTAP plus school closure or prevaccination plus school closure gains 51 QALYs **QALYs per 1000 population, incremental** FTAP and school closure and the intervention of prevaccination and school closure contributed to the most incremental QALYs (262) **Deaths per 1000 population** Pre-vaccination intervention was the most effective strategy. Only 1 death/1000 population occurred via this strategy. On the other side, most deaths have been seen in case of no intervention (13 deaths/1000 population) and FTAP25 with 12 deaths. **Number of cases** Full TAP is the most effective single strategy, reducing the number of cases by 54% Pre-vaccination reduces the number of cases by 48% Adding school closure to full TAP or pre-vaccination further improves health outcomes
Yarm and et al. 2010	Self-isolation and mandatory quarantine Vs. vaccination	**Effectiveness in low-levels of interventions** Vaccination is more effective than self-isolation. **Effectiveness in high-levels of interventions** Self-isolation is more effective than vaccination. This has been shown due to weaknesses of vaccinations, such as delays in effectiveness.
Halder et al. 2011	Antiviral drugs combined with limited duration school closure Vs. 1. School closure as a sole intervention alone and as dual, triple, quadruple strategy 2. Other social distancing strategies, such as reduced workplace attendance	**The illness attack rate of interventions (symptomatic)** The illness attack rate ranges from 2.4% (SD 0.37) to 8.5% (SD 1.1) while that of the unmitigated attack rate is 13% (SD 0.9). The individual school closure for 2 weeks along with the continuous – 50% workplace closure, antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis showed the lowest illness attack rate (2.4%). This combination is the most effective intervention. Short-duration school closure is less effective (6.5 to 8.2 illness attack rate) Continuous school closure is more effective, with an attack rate of 3.2.

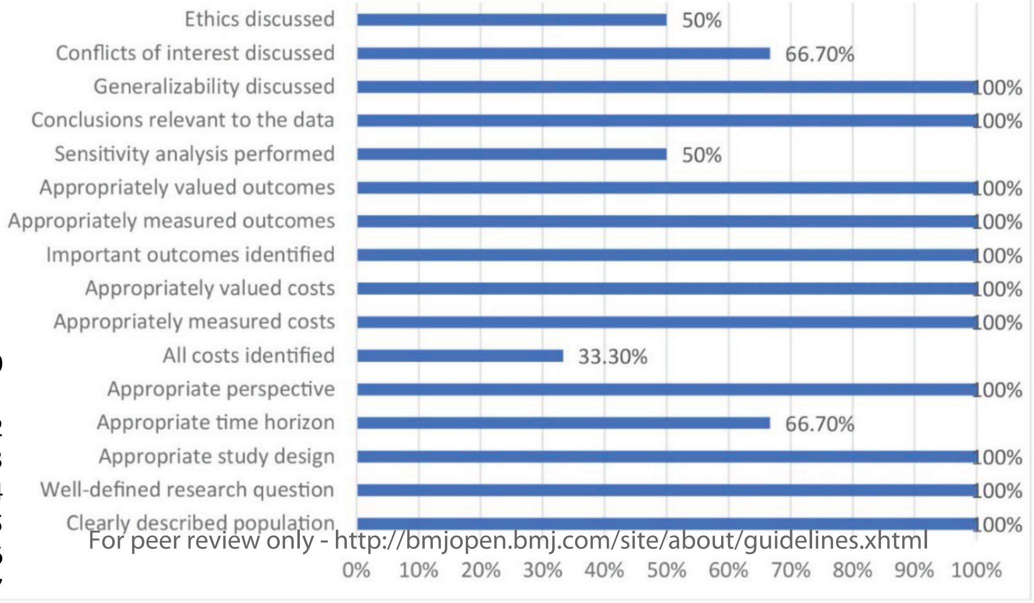
Orset 2018	Home confinement Vs. No intervention	**Incidence rate reduction by the home confinement intervention** There are studies that indicate the higher the compliance rate regarding home confinement, the higher the reduction of the incidence rate of influenza will be. More particularly: In case of a 70% compliance rate: 83% reduction of incidence rate In the case of 80% compliance rate: 91% reduction of incidence rate The compliance rate with home confinement is between 75.90 and 94.44%, for this study. **Rate reduction threshold in the incidence due to intervention** The higher the proportion of all cases complying with home confinement, the higher the reduction rate of the threshold for VSL will be. For example: In case of 49.24% of all cases complying with home confinement: €7.65 million Threshold for VSL In case of 51.39% of all cases complying with home confinement: €5.06 million Threshold for VSL
Trach t t al. 2012	Mask wearing group Vs. No intervention	**When there are no interventions (no masks worn)** **Cumulative number of cases/ based on three scenarios - R avg/unc[*]** In the case of 1.25; A total of 101,424,384 cases. Most of them identified at 18-64 age group. In the case of 1.3; A total of 117 673 024 cases. Most of them identified at 18-64 age group. In the case of 1.35; A total of 130 043 351 cases. Most of them identified at 18-64 age group. **Hospitalizations** Based on three different scenarios - R avg/unc: 1.25, 1.3, and 1.35 In the case of 1.25: For all age groups, a total of 3 275 616 hospitalizations have been estimated. 75.8% of them found to be in 18-64 ages In the case of 1.3: For all age groups, a total of 3 793 350 hospitalizations have been estimated. 74.8% of them found to be in 18-64 ages In the case of 1.35: For all age groups, a total of 4 184 352 hospitalizations have been estimated. 73.7% of them found to be in 18-64 ages **Deaths** More deaths have been found in ages 18-64, both in three scenarios, and more than 90% of the total deaths (281 319-349 578)

		As a result, the model showed that in case of 10% of the population wearing masks with an effectiveness of 20% in reducing susceptibility and infectivity, there is a large reduction in the cumulative number of cases.

PCP: Primary care physician, YLL: Yearls of life lost, VSL: Value of statistical life, QALY: Quality-adjusted life year, FTAP: Full-targeted antiviral prophylaxis, SD: Standard deviation,

* Average effective reproduction number (uncontrolled)


*Studies related to preparedness measures of infectious respiratory disease outbreaks
Lankelma et al. (2019) 79%
Orset (2018) 58%
Saunders-Hastings et al. (2017) 100%
Tracht t al. (2012) 74%
Halder et al. (2011) 95%
Yarmand et al. (2010) 84%
Khazeni et al. (2009) 90%
Sander et al. (2009) 79%
Sadique et al. (2008) 84%
Balicer et al. (2005) 74%
Madema et al. (2004) 84%
**Studies related to cost of infectious respiratory disease outbreaks
Prager et al. (2017) 88%
Morales-Suárez-Varela et al. (2016) 88%
Silva et al. (2014 94%
Higgins et al. (2011) 94%
Wilson et al. (2009) 88%
Rodríguez-Rieiro et al. (2009) 75%
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%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50%
Conflicts of interest discussed
66.70%
Generalizability discussed
100%
Conclusions relevant to the data
100%
Sensitivity analysis performed
50%
Appropriately valued outcomes
100%
Appropriately measured outcomes
100%
Important outcomes identified
100%
Appropriately valued costs
100%
Appropriately measured costs
100%
All costs identified
33.30%
Appropriate perspective
100%
Appropriate time horizon
66.70%
Appropriate study design
100%
Well-defined research question
100%
Clearly described population
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0%
10%
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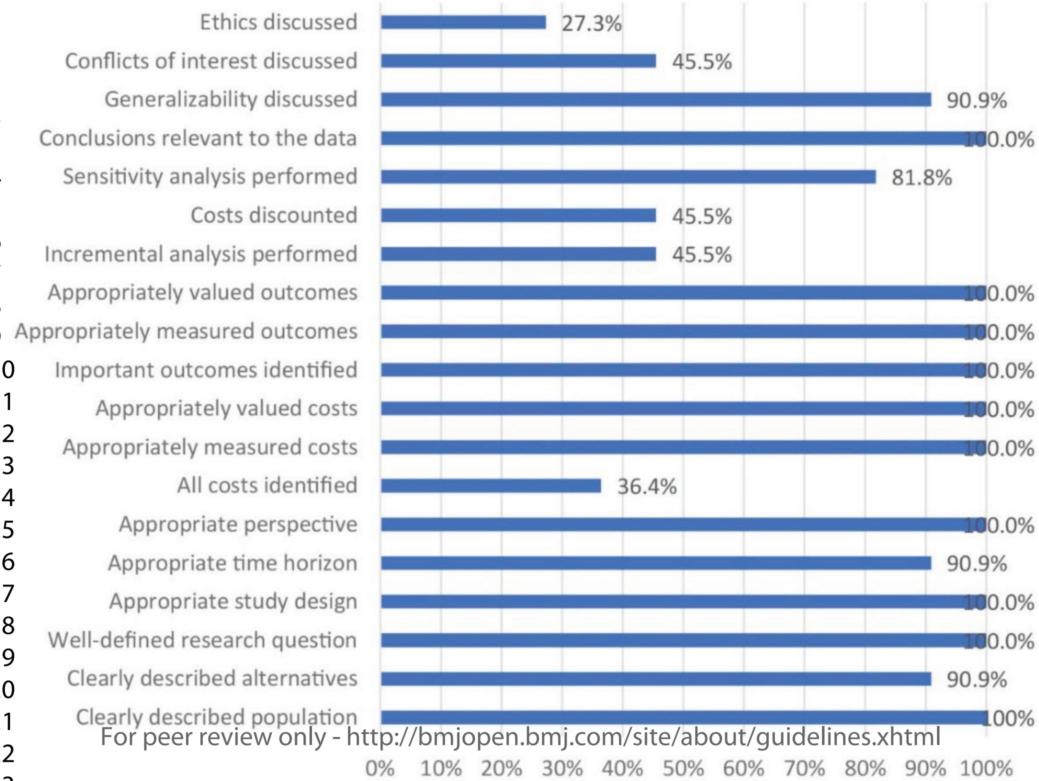
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Conflicts of interest discussed
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Generalizability discussed
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Sensitivity analysis performed
81.8%
Costs discounted
45.5%
Incremental analysis performed
45.5%
Appropriately valued outcomes
100.0%
Appropriately measured outcomes
100.0%
Important outcomes identified
100.0%
Appropriately valued costs
100.0%
Appropriately measured costs
100.0%
All costs identified
36.4%
Appropriate perspective
100.0%
Appropriate time horizon
90.9%
Appropriate study design
100.0%
Well-defined research question
100.0%
Clearly described alternatives
90.9%
Clearly described population
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BMJ Open

Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045113.R1
Article Type:	Original research
Date Submitted by the Author:	25-Jan-2021
Complete List of Authors:	Vardavas, Constantine; University of Crete, School of Medicine Nikitara, Katerina; University of Crete, School of Medicine Zisis, Konstantinos; University of Crete School of Medicine Athanasakis, Konstantinos; University of West Attica, Department of Public Health Policy, School of Public Health Phalkey, Revati ; University of Nottingham School of Medicine, Division of Epidemiology and Public Health Leonardi-Bee, Jo; University of Nottingham School of Medicine, Division of Epidemiology and Public Health Johnson, Helen; European Centre for Disease Prevention and Control, Epidemiological Methods Tsolova, Svetla; European Centre for Disease Prevention and Control Ciotti, Massimo; European Centre for Disease Prevention and Control Suk, Jonathan; European Centre for Disease Prevention and Control
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Health economics, Public health
Keywords:	INFECTIOUS DISEASES, HEALTH ECONOMICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES

Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis

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ABSTRACT

OBJECTIVES: Respiratory infectious disease outbreaks pose a threat for loss of life, economic instability, and social disruption. We conducted a systematic review of published econometric analyses to assess the direct and indirect costs of infectious respiratory disease outbreaks that occurred between 2003 and 2019.

SETTING: Respiratory infectious disease outbreaks or public health preparedness measures or interventions responding to respiratory outbreaks in OECD countries (excluding South Korea and Japan) so as to assess studies relevant to the European context. The cost-effectiveness of interventions was assessed through a Dominance Ranking Matrix approach. All cost data were adjusted to the 2017 Euro, with interventions compared to the null. We included data from 17 econometric studies.

PRIMARY AND SECONDARY OUTCOME MEASURES: Direct and indirect costs for disease and preparedness and/or response or cost-benefit and cost-utility were measured.

RESULTS: Overall, the economic burden of infectious respiratory disease outbreaks was found to be significant to healthcare systems and society. Indirect costs were greater than direct costs mainly due to losses of productivity. With regards to non-pharmaceutical strategies, prehospitalization screening and the use of protective masks were identified as both an effective strategy and cost-saving. Community contact reduction was effective but had ambiguous results for cost saving. School closure was an effective measure, but not cost-saving in the long term. Targeted antiviral prophylaxis was the most cost-saving and effective pharmaceutical intervention.

CONCLUSIONS: Our cost analysis results provide evidence to policymakers on the cost-effectiveness of pharmaceutical and non-pharmaceutical intervention strategies which may be applied to mitigate or respond to infectious respiratory disease outbreaks.

ARTICLE SUMMARY

Strengths and limitations

- A systematic approach was followed, and the assessment of data quality indicated that the majority of studies included were of high quality.
- The synthesis of the results was performed using the DRM approach, which allowed for a direct comparison of the cost-effectiveness of each intervention to the null.
- Costs and resources varied between different countries, different regional settings, and over time, making the cost component comparison of cost-effectiveness measures complex to interpret.
- We only focused on EU and OECD analogous countries excluding Japan and South Korea, and hence our cost-effectiveness analyses are not applicable to other countries or settings.
- Discrepancies in context and populations likely affect the implementation and efficacy of interventions.

MAIN TEXT

INTRODUCTION

Emerging, re-emerging and endemic respiratory and influenza-like infectious diseases represent a threat for loss of life, economic instability and social disruption as they can rapidly spread within communities and across countries, affecting the whole globe. Annually, it is estimated that 5–15% of the population will suffer from influenza-related respiratory tract infections, while 3–5 million people face severe illness due to influenza (1). In 2018, a total number of 109.5 million influenza virus episodes were identified among children under five years globally, with approximately 34 800 overall deaths. In Europe, seasonal influenza is estimated to lead to 4 -50 million symptomatic cases, and 15,000 – 70,000 deaths annually, however this may differ between years, as the severe 2017/2018 influenza season led to an estimated 152,000 deaths in Europe alone (2, 3).

In order for robust national preparedness systems and response strategies to outbreaks to be established in the Europe, it is crucial for public health officers to receive recent data of the health impact and the economic burden of respiratory infectious disease outbreaks in contrast to emergency response and preparedness actions. This evidence will ensure well-informed decisions regarding, among others, the proper allocation of resources (4, 5). To this extent, although there is substantial literature from previously published systematic reviews on the value of public health emergency preparedness, they either refer to an older timeframe (6) or use mathematical models to predict the effectiveness and cost-effectiveness of measures (7). Hence there is limited recent information on the economic evaluations of infectious respiratory disease outbreaks that provide an overview of the cost effectiveness of response measures (8).

Within the above context, the aim of this systematic review of econometric analyses was to assess the economic impact of response and preparedness measures when contrasted with the cost of infectious respiratory disease outbreaks. We further synthesize the cost-effectiveness for each intervention using a Dominance Ranking Matrix (DRM) approach.

METHODS

Search strategy and selection criteria

A comprehensive systematic literature review of published econometric analyses was conducted between July-August 2019 using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (9) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (10) to identify peer-reviewed articles using two biomedical literature databases (PUBMED and EMBASE) and two economic literature databases (ECONLIT, IDEAS REPEC). The search strategy was designed for a broader study aiming to identify econometric studies on all types of infectious diseases, but due to the outbreak of COVID-19, and for the purposes of this specific article we retained only those referring to respiratory infectious diseases.The complete search strategy and search terms is available in **Appendix 1**.

The inclusion criteria were as follows:

- ✓ Exposure: Respiratory Infectious disease outbreaks or public health preparedness measures or interventions responding to respiratory outbreaks in OECD countries (excluding Asian countries South Korea and Japan due to the wide cultural differences with the EU contextas this study was performed under contract for the European Center for Disease Control and Prevention
- ✓ Comparator: i) No intervention (cost of inaction) or current practice, ii) Cost of preparedness vs cost of response (for studies reporting cost and benefit of public health preparedness)

- ✓ Outcome measures: Direct and indirect costs for disease and preparedness and/or response or cost-benefit and cost-utility. Typical outcome measures of economic evaluations included: Life years gained or cost per life-year gained with the intervention under investigation when incremental costs are combined, cost per Quality-Adjusted Life Year (QALY) gained, cases averted, monetary outcomes
- ✓ Perspective: All direct and indirect costs pertaining to all relevant perspectives (e.g. individual, hospital, insurance and societal- including national and regional) and All direct and indirect costs pertaining to all relevant perspectives according to York Health Economics Consortium (11) (health system perspective, including hospital, public health units; societal perspective; governmental perspective)
- ✓ Study designs: All relevant analytical epidemiological designs which estimate cost either as full economic evaluation studies, including cost-minimization, cost-effectiveness, cost-utility and cost-benefit studies; cost-outcome and economic modelling studies; or partial economic evaluations;
- ✓ Timeframe: From 2003 until August 2019, to reflect the timepoint from the 2003 SARS outbreak and onward (12) – this review refers to the pre-COVID-19 published evidence.

Studies that met the above inclusion criteria but did not report or perform any econometric analysis were excluded.

Data analysis and extraction

Studies identified from the searches were uploaded into a bibliographic database in which duplicate entries were removed. Initially, a pilot training screening process was used, where a random sample of 100 titles and abstracts were screened independently for eligibility by four reviewers (KN, KZ, RP, JLB) to enable consistency in screening and identify areas for amendments in the inclusion criteria. Following this, a random sample of 50% of titles and abstracts was screened independently by two reviewers. Since a high measure of inter-rater agreement was achieved (percentage agreement > 88·7% and/ or Cohen's Kappa >0·646), the remaining titles and abstracts were screened for eligibility by one reviewer. Where insufficient information was available in the title and abstract to make a decision, the full-text article of the document was retrieved for further inspection. Full-text documents of potentially eligible studies were retrieved for the records marked for inclusion. All full-text documents were independently double-screened by two reviewers, and inter-rater agreement measures were calculated at 88·3%. Disagreements in every step of the process were subsequently discussed and agreed upon. Documents that passed the inclusion criteria on the basis of the full-text screening were included in the current review.

Appraisal of methodological quality

For evaluating the methodological quality of the includedstudies , the Consensus on Health Economic Criteria (CHEC) checklist (13) was used. This specific tool has been designed for the assessment of full economic evaluations and includes 19 items (questions) with answers of "Yes" or "No". For each positive answer on full economic evaluation studies, a single point was being assigned for the methodological quality, with a maximum score of 19. For the quality appraisal of partial economic evaluations, we used items from the CHEC checklist that were applicable – hence the maximum score was 16. The quality appraisal process was completed by two reviewers, with a percentage of agreement in the three pilot studies, initially assessed by both, of 83·7%.

Comparative economic analysis approach

All cost data were adjusted to a common currency (Euro in 2017 -€^{2017}) and price year; using the Campbell and Cochrane Economics Methods Group–Evidence for Policy and Practice Information and Coordinating Centre cost converter (14). We adjusted the original estimate of cost from the original price year to a target price year of the Euro in 2017 (€^{2017}), using a Gross Domestic Product deflator index (GDPD), obtained from the International Monetary Fund World Economic Outlook Database GDPD index data set (15). Subsequently, we converted the price-year adjusted cost estimate from the original currency to €^{2017}, using conversion rates based on Purchasing Power Parities (PPP) for GDP. (The 2017 implied conversion factor was USD 1 = € 1·13, the €^{2017} conversion factor was €1= 1·2 USD, while with regards to British pounds, the conversion factor was £1 = € 0·88). PPP values adjust appropriately for differences in current price levels between countries, thus allowing comparisons based on a common set of average international prices; this is an advantage over pure exchange-rate conversions and GDP per capita approaches as PPPs eliminate differences in price levels between countries in the process of conversion. For studies that did not state the year of cost calculation, the costs were calculated one year before the publication year of each respective study.

Synthesis of cost-effectiveness

In order to synthesize the cost-effectiveness results, the Dominance Ranking Matrix (DRM) approach was used, which is a classification system developed for summarizing and interpreting the results of economic evaluations in systematic reviews (16). The DRM is a three-by-three matrix with the following classification options:

(a) Strong dominance for the intervention when the incremental cost-effectiveness measure shows the intervention compared with no intervention as: (i) more effective and less costly; or (ii) as effective and less costly; or (iii) more effective and equal cost.

(b) Weak dominance for the intervention when the measure shows the intervention compared with no intervention as: (iv) effective and equally costly; or (v) more effective and more costly; or (vi) less effective and less costly.

(c) Non-dominance for the intervention when the measure shows the intervention compared with no intervention as: (vii) less effective and more costly; or (viii) less effective and equally as costly; or (ix) as effective and more costly.

Within our DRM only studies that compared interventions to no intervention were included in the matrix.

Patient and public involvement

This study was performed under contract for the European Center for Disease Control and Prevention. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

The initial study search yielded 20 513 studies after removal of the duplicates and according to the specified selection criteria,only 66 were further assessed for eligibility via full text. Through the assessment of the full-texts, 52 studies were excluded for the following reasons: inadequate data on costs and/or cost-effectiveness (n=2), they were reviews (n=15), not referring to respiratory outbreaks (n=29), not referring to outbreaks of infectious diseases (n=2) and conference abstracts with no full text available (n=4). Additionally, three full-text papers were identified through the screening of the reference lists of the selected manuscripts, and hence, a total number of 17 econometric studies were considered in our analysis. The flowchart of the study selection process is presented in **Figure 1.**

Overall, 11 out of the 17 studies were of high methodological quality (>80%), five were categorized as of good quality (60%-80%), and only one was of medium quality (40%-60%) due to missing quality criteria not mentioned by the authors including the comparative intervention, sensitivity analysis, incremental costs & outcomes. **Appendix 2** presents the overall quality appraisal score, for studies related to cost of infectious disease outbreaks, and for sources related to preparedness, preventive and response measures concerning infectious disease outbreaks. The quality appraisal of partial and full economic evaluation studies respectively is in **Appendix 3 and Appendix 4** respectively. It is important to note that for the studies where a partial economic evaluation was performed, we only performed calculations for the items of the quality appraisal tool that were applicable.

Comparative cost analysis of infectious respiratory disease outbreaks

Regarding infectious respiratory disease outbreaks, six studies were included (17-22). All studies referred to influenza as the disease, either relating to pandemic H1N1 or seasonal Influenza B. Geographically the studies were performed in the USA (17), Spain (18, 22), France (19), New Zealand and Australia (20, 21). Five out of the six studies were observational in design (cross-sectional or retrospective) and used collected data (18-22); one study was based on a simulation model (17). Similarly, five out of the six studies assessed costs from a healthcare system perspective (17, 18, 20-22); however, societal (n=3) (17-19) governmental (n=1) (17) and payer (n=1) (19) perspectives were also assessed. Discounting in costs was not necessary for any of the included studies as the implementation timeframe had a duration of less than one year, and sensitivity analyses were performed only in three studies (17, 19, 21). A detailed description of the characteristics of the included illness studies is presented in **Appendix 5**.

Table 1 presents an analytical overview of the direct and indirect costs associated with influenza outbreaks. Direct costs mainly refer to medical and healthcare costs related to the outbreaks, along with the costs of response measures. Indirect costs included the loss of income, the loss of business, and the loss of productivity. The overall direct costs reported in the studies where calculated at the patient level where possible.

The most recent study was a simulation study by Prager et al. (17), in which multiple scenarios were assessed through simulation models for the US population so as to estimate the total economic burden of pandemic influenza outbreaks in the US, taking into account both the scenario of an adequately vaccinated population and the opposite. The results indicated that medical expenditures for a pandemic influenza outbreak could reach 83·2 billion, €^{2017} in the no vaccination scenario, and 67·3 billion €^{2017} in the vaccination scenario. Notably, for indirect cost estimations, vaccination in a pandemic scenario would reduce workday losses by 22·2 million days, when compared to no vaccination.

Silva et al. (2014) (19) focused on an influenza outbreak in France between 2010 and 2011 and extrapolated the results to the entire country with a hypothetical approximate number of 2 million influenza cases (3·2% of the French population), for which they calculated an overall cost of 151 million €^{2017} for the French Health Insurance System. Direct costs per patient ranged between 35·26

€[2017] and 73·91 €[2017], with higher indirect costs of 97·88€[2017] per day due to absence from work, for those within the 15-65 age group.

Two studies assessed the cost of an influenza outbreak from an intensive care unit (ICU) and hospital perspective (20, 21). One focused on ICU and hospital costs derived from an influenza pandemic in 2009 in New Zealand (among 1224 cases, of which 122 were admitted to ICUs), which surpassed 40·8 million €[2017]at an average cost of 32 167 €[2017]per patient, with significantly increased costs for patients with underlining comorbidities (21). The mean total hospitalization cost (normal and ICU) per case surpassed 53 553 €[2017]. Similarly, in a study that included 762 H1N1 cases from both Australia and New Zealand, the mean cost per ICU patient was 61 368 €[2017], with a per-day cost of 4 767 €[2017] (20). On the contrary, the non-ICU patient had a mean cost of 10 755 €[2017], however, overall non-ICU patient costs surpassed those of ICU patients (12·96 Million €[2017] vs 6·1 million €[2017]), leading to a total hospitalization cost of 19·3 million €[2017] for the 2009 influenza outbreak.

Similarly, Rodriquez-Rieiro et al. (2009) (22) studied the hospitalisation costs occurred during the 2009 influenza pandemic in Spain, which reached 36·7 million €[2017] for 11 449 hospitalisations– during which the appearance of comorbidities led to higher average costs per patient (2 205 €[2017] vs 1 172€[2017] respectively). Specific populations in Spain were assessed by Morales-Suárez-Varela et al. (2016) (18) who estimated direct costs for medical visits, medication and diagnostic tests at €3 908 €[2017] for non-pregnant women and 2 227€[2017] for pregnant women of reproductive age, with indirect costs estimated at 107€[2017] and 64 €[2017] respectively.

Cost-effectiveness studies of measures in averting and/or responding to infectious respiratory disease outbreaks

We identified 11 studies (23-33) referring to *preparedness, preventative and response measures*, to influenza outbreaks, presented in detail in **Appendix 6**. Two studies were observational (based in the Netherlands and the UK) (23, 24), and the remaining nine were simulation models (four US models, with one study each modelled for Canada, France, Australia, Israel and one referring to developed countries in general). All included studies either used a cost-effectiveness or a cost-utility economic evaluation approach. The studies' timeframes ranged from 2004 to 2018. Regarding the perspective for direct and indirect costs, a healthcare system or society approach was consistently presented.

The preparedness, preventive and response measures described included three pharmaceutical interventions (vaccination as a response measure, general vaccination, antiviral drug therapy and stockpiling) (31-33), four non-pharmaceutical interventions (screening at the point of contact, community contact reduction, volunteer isolation/quarantine, school closure and the use of personal protective measures) (23-25, 28) and four combined pharmaceutical and non-pharmaceutical interventions (26, 27, 29, 30). **Table 2** presents the details of the cost-effectiveness studies on preparedness and response measures for infectious respiratory disease outbreaks. Further details on the comparative analysis of health indexes gained when adverting or responding to respiratory outbreaks can be found in **Appendix 7.**

With regards to studies that compared multiple interventions, a simulation model of pandemic influenza in the USA that studied the cost-effectiveness of stockpile strategy identified that expanded adjuvanted vaccination seemed to be the most cost-effective strategy, averting 68% of infections and deaths and gaining 404 303 QALYs at $10 844 (€9 600 €[2017]) per QALY gained relative to the stockpiling strategy (30). Saunders-Hastings et al. (2017) (26), using a simulated population of 1·2 million people, (reflective of Ottawa, Canada), performed a cost-effectiveness analysis of six interventions including vaccination, school closure, antiviral prophylaxis and other measures. The authors concluded that vaccinationwas the most cost-effective intervention when compared with other interventions while the least cost-effective intervention was school closure in conjunction with community-contact reduction, personal protective measures, voluntary isolation and quarantine. In particular, the cost per life-year saved was estimated to be $2 581 (1 700, €^{2017}) for combined vaccination and antiviral treatment, while an estimated cost of $260 472/life-year saved (€171 590 €^{2017}) was noted for school closure in conjunction with other interventions. Finally, Halder et al. (2011) (27) aimed to evaluate, the most cost-effective strategies suitable for a future pandemic with H1N1 2009 characteristics, in Australia. The results showed that the strategy with the lowest cost was the dual strategy of individual school closure for two weeks along with antiviral drug strategies, with a total cost of approximately AU$632 (376·31€^{2017}) per case averted. The strategy with the highest cost was the dual strategy of school closure along with the continuous – 50% workplace closure, with a cost of $103 million (61·3 million€^{2017}), per 100 000 population.

Comparative cost-effectiveness analysis

A Dominance Ranking Matrix (DRM) approach is presented in **Figure 2**. These interventions include both pharmaceutical measures and non-pharmaceutical measures. The interventions were compared to the "no intervention" scenario, with the exception of one study (29) in which the comparators were vaccination vs self-isolation, which was subsequently excluded from the DRM.

Pharmaceutical measures

Vaccination as a response measure

With the application of our inclusion and exclusion criterea, four studies assessed vaccination as a response measure in the context of an outbreak and included a cost analysis. Overall, as highlighted in the majority of the studies, vaccination as a response measure was noted to have a more significant clinical effect than comparators and was more cost-saving in most cases. According to Sander et al. (2009) (30), the most clinically effective intervention was expanded adjuvant vaccination which contributed to 404 030 QALYs. Similarly, Khazeni calculated that with expanded adjuvanted vaccination, 45 941 deaths would be averted (31). Additionally, Saunders-Hastings et al. (2017) (26) concluded that the most cost-effective approach for controlling a pandemic was vaccination in combination with antiviral therapy and prophylaxis. However, a review of the results showed that much of the cost-effectiveness of pharmaceutical interventions were driven by vigorous vaccination campaigns, while the contribution of antiviral drugs' was not of significance. Finally, Madema et al. (2004) (33) through a simulation model of an influenza pandemic among developing countries calculated the costs and assessed the effectiveness of two types of vaccines, an egg-based and a cell culture-based, in comparison with no intervention. Overall, vaccination was more cost-effective than no intervention; however, vaccination with cell culture-based vaccines was the most cost-effective strategy with a cost of 3 779 €^{2017} per life-year gained. General vaccination was also assessed by Sander et al. (2009) (30), who noted it to be both more cost-saving and effective than the unmitigated pandemic scenario, although when comparing prevaccination with low-efficacy vaccines with full targeted antiviral prophylaxis, it was less effective and more costly.

Antiviral drugs

Antiviral drug strategies were assessed in five studies, where it was noted that they were both more effective and cost-saving than the no intervention scenario, primarily when used as targeted prophylaxis. According to Halder et al. (2011) (27), antiviral drug strategies such as antiviral treatment and antiviral treatment in combination with household confinement and extended prophylaxis can result in reduced attack rates of 7.6% and 3.5% in comparison to the unmitigated attack rate of 13%. The costs of these strategies are also lower than the cost of no intervention.

Moreover, therapeutic treatment and postexposure prophylaxis for exposed individuals (targeted prophylaxis) were shown to be the most cost-saving (32). Consistent with the above, antiviral therapy in combination with a layered non-pharmaceutical approach, seemed to reduce the overall economic costs the most and was identified as more effective when compared with no intervention (26). Furthermore, it was noted that expanded antiviral prophylaxis could help delay a pandemic when additional strategies are implemented, and would also lead to averting 32 745 deaths in the US.[31] Finally, Sander et al. (2009) (30) used a stochastic simulation model of pandemic influenza in the USA, aiming to evaluate the potential economic impact of 16 different mitigation interventions from a societal perspective. Conclusively, targeted antiviral prophylaxis was both the most cost-saving and effective intervention with a cost of \$127 per capita (€118·73 €^{2017}), with the scenario of implementation of expanded antiviral prophylaxis leading to a total of 282 329 QALYs gained.

Stockpile strategy

The stockpile strategy was assessed in three of the studies included in this systematic review. Based on the findings, stockpiling antiviral prophylaxis in the context of a pandemic was noted to be both cost-saving for the society, and avert loss of life compared to no intervention (30). Moreover, pre-pandemic stockpiling of antiviral drugs would be more effective and cost-saving than no intervention if antiviral drugs were administered either solely as a treatment or as short-term prophylaxis for exposed individuals (32). Finally, stockpiling was also found more effective than a no intervention scenario (averting 29 761 deaths in the US), although when compared with other interventions, expanded vaccination and prophylaxis were found to be more effective (31).

Non-Pharmaceutical measures

Pre hospitalisation screening

Lankelma et al. (2019) (23), assessed the cost-effectiveness of screening patients with acute respiratory tract infection for influenza before hospital admission. Overall costs of screening were estimated at 98 968€^{2017} for 1 546 tests and 624 cases and reported net savings of 388 317€^{2017} for the healthcare system. Point-of-care testing for influenza before hospital admission was identified as a cost-effective intervention (23).

Community contact reduction

Community contact reduction was assessed in two studies, where it was either implemented solely or in combination with other pharmaceutical and non-pharmaceutical measures. Home confinement was noted as cost-effective as a preventive measure in the context of influenza epidemics, if the proportion of compliance is adequate and infected individuals ask for medical assistance, regardless of the severity level of the pandemic (26). Isolation of infected individuals was found to be among the most effective interventions, whereas combined with community contact reduction, personal protective measures and antiviral treatment, self-isolation had the lowest cost (27).

School closure

The effectiveness and the economic burden of school closure were evaluated in four studies, highlighting that the duration of school closure and potentially combined strategies significantly affect its impact. Sadique et al. (2008) (24) estimated the economic burden of school closure in the UK from a societal perspective, and showed that the estimated costs of school closure were high, at 0·28 - 1·68 billion, €^{2017} per week and the authors concluded that school closure was likely to significantly add an extra economic burden on the health system through staff absenteeism, even if school closure may delay infectious disease transmission. Similarly, Sander et al. (2009) (30), who studied school closure as an additional intervention to full targeted antiviral prophylaxis or prevaccination found that while school closure further improves health outcomes (gaining 51 QALYs), it was the least cost-effective measure as it increased the total cost to society by $2 700 per capita (€2 524 €^{2017}). Additionally, school closure produced only a small reduction in attack rate, whether implemented in combination with other interventions or alone (26). Finally, exclusive school closure for two weeks along with the continuous 50% workplace closure, antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis, had the lowest illness attack rate (2·4%) and one of the lowest costs. On the contrary, school closure as a sole intervention to counterbalance infectious respiratory diseases was not a cost-effective measure (27).

Personal protective measures

Personal protective measures such as face masks and hand hygiene were assessed in two of the included studies, noting that they could contribute to the control of a pandemic, dependant though on the exposed and susceptible individuals' compliance rate, the setting and the overall burden of the respiratory pandemic (26, 28). Tracht et al. (2012) aimed to assess the cost-effectiveness of facemasks (N95 grade) in reducing the spread of pandemic (H1N1) 2009, using a simulation model of the US population and identified an economic burden of 728·28 billion €^{2017} (incl. direct and indirect costs). Notably, if masks are worn by 10% and 50% of the adult population of the US net savings were calculated at 418·75 billion €^{2017}and 501·9 billion €^{2017} respectively. Hence, the use of face masks were identified as a cost-effective preventive measure depending on the population's level of compliance.

DISCUSSION

The aim of this systematic literature review of econometric analysis studies was to assess the economics of preparedness when contrasted with the cost of infectious respiratory disease outbreaks primarily within the context of European and OECD countries (excluding Japan and S Korea). Overall, the economic burden of infectious disease outbreaks is costly to healthcare systems, or to governments and society reflecting the medical costs for response activities including both the treatment of the confirmed cases and the surveillance and elimination of the disease's transmission, as well as indirect costs which were also substantial.

In general, the majority of direct costs seemed to primarily reflect cost of additional personnel hours, which are mandatory for the management of the infected cases, for the organisation of response planning and contact tracing, for providing educational training and materials, as well as laboratory costs. With regards to indirect costs, these could in many cases be greater than the direct costs, especially when school closures and/or workplace closures are enacted across a population, which in turn impact productivity and increase the economic burden.

While all the identified pharmaceutical and non-pharmaceutical interventions lead to a health benefit for the individual or the society, the cost benefit of such interventions differs. With regards to the potential non-pharmaceutical strategies, we identified that the use of personal protective measures, such as a facemask, is both cost-saving and effective, as also is pre-hospitalization screening among suspect cases. On the other hand, all studies that assessed the impact of school closure noted that although it is an effective measure in reducing transmission, it is not cost-saving as it leads to increased economic burden. Moreover, when school closure was used as a sole intervention, then the use of limited duration school closure was significantly more cost-effective compared to continuous school closure (24). Community contact reduction was identified to have a positive health impact but had ambiguous results with regards to its potential cost saving as one study (26) noted that it is a cost-saving intervention, while the other (27) noted that social distancing strategies, such as reduced workplace attendance, were not a cost-saving measure primarily due to productivity losses, especially during longer periods of closure. Productivity losses primarily were noted to arise from pandemic related deaths and illness coupled with those losses due to interventions such as workplace closure and child-care of an ill child. It is important to note that non-pharmaceutical strategies were mostly applied complementary with a pharmaceutical measure or in combination with other non-pharmaceutical strategies in order to enhance their effectiveness. However, their cost-effectiveness highly depended on the duration, the level of compliance from the population and the type and burden of the infectious disease. It should moreover be noted that cost-effectiveness of measures will vary depending on the epidemiology of the disease in question.

With regards to pharmaceutical interventions, vaccination as a rapid response measure for infected and suspected individuals was noted to have a more significant clinical effect than comparators and was more cost-saving in most cases. As for antiviral treatment, the majority of the findings noted that it is a cost-effective strategy, especially when combined with other pharmaceutical and non-pharmaceutical interventions or when used as targeted prophylaxis for exposed individuals. Targeted antiviral prophylaxis was the most cost-saving and effective intervention, while stockpiling was cost saving in most cases and averted loss of life when compared to no intervention.

The current number of economic evaluation or cost-effectiveness studies of influenza outbreak preparedness measures is small, with an increase shown since the 2009 influenza pandemic, however it is important to note that these studies refer to the evidence published before the COVID-19 outbreak. There are only a limited number of related reviews, however of different scope focusing primarily on policy recommendations (34) or used dynamic transmission models in the included economic assessments of pandemic influenza preparedness measures based on significantly older studies (6). Additionally, most of the existing review studies either evaluate the overall economic burden of the disease or the cost-effectiveness of different pharmaceutical and non-pharmaceutical interventions without necessarily them reflecting the economics of outbreaks of infectious respiratory diseases.

Placing the above into context and following the assessment of the methodological approaches used across studies it is essential to note what are the minimum contents that economic outbreaks of respiratory studies should include that would help inform future and upcoming work, especially in light of the COVID-19 pandemic. These include the clear noting of the study year, the population at risk and population infected, the type of economic perspective (i.e. healthcare, societal etc.), timeframe and discounting as well as detailed reported direct and indirect costs of the respiratory outcome and the interventions were applied.

Strengths and limitations

A significant strength of this review is the comprehensive approach that was followed and the assessment of data quality - which indicated that the majority of the studies included were of high quality. Secondly, the synthesis of the results was performed using the DRM approach, which allowed for a direct comparison of the cost-effectiveness of each intervention to the null intervention.

However, there are a few limitations, firstly, costs and resources varied between different countries, different regional settings, and over time, making the cost component comparison of cost-effectiveness measures complex to interpret. Moreover, we only focused on EU and OECD analogous high-income countries excluding Japan and South Korea, and hence our cost-effectiveness analyses are not applicable and generalizable to other countries and particularly middle- and low-income countries. Additionally, discrepancies in context and populations likely affect the implementation and efficacy of interventions, undermining even the effectiveness elements comparability in the cost-effectiveness measures, especially in complex multi-component public health interventions. In addition, our study did not include studies published before 2003,or after 2019. Also, it should be noticed that publication bias may exist due to the English language restriction applied. . Another limitation to be noted is that this review excluded seasonal influenza outbreaks since these occur on a yearly basis. Furthermore, this study was performed before the impact of COVID-19 and hence reflects the published knowledge before the current pandemic.

CONCLUSION

The value of this systematic review of econometric studies is to provide a synthesis of the evidence of the cost of respiratory infectious disease outbreaks and the cost-effectiveness of specific interventions that can be applied in response. Furthermore, our assessment identifies a minimum number of econometric measures which should be recorded during the reporting of respiratory infectious disease outbreaks that would aid future decision making. Our cost analysis results give evidence to public health policymakers, primarily in the EU or the US, as to the cost-effectiveness of a range of pharmaceutical and non-pharmaceutical intervention strategies which may be applied to mitigate or respond to infectious respiratory disease outbreaks.

ACKNOWLEDGEMENTS

We would like to thank Ioanna Lagou and Chrysa Chatzopoulou for contributing to data management.

CONTRIBUTORS

CV, JLB, ST and JES designed the study. KN and KZ undertook the literature review and extracted the data with help from JLB and RP. JLB and RP developed the search code. KZ, KN and KA analysed and interpreted the econometrics data. HJ and MC participated in data evaluation and interpretation along with CV, JLB, RP, JES, KN, KZ, KA, and ST. CV and KN wrote the first draft of the manuscript with input from all authors. All authors reviewed and revised subsequent drafts.

Declaration of interests

We declare no competing interests.

Funding

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), to the PREP-EU Consortium, coordinated by Dr. Vardavas under specific contract No. 1 ECD.9630 within Framework contract ECDC/2019/001. The information and views in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Commission/Agency. The Commission/Agency do not guarantee the accuracy of the data included in this study. Neither the Commission/Agency nor any person acting on the Commission's/Agency's behalf may be held responsible for the use which may be made of the information contained therein.

Data sharing statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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TABLES

Table 1. Characteristics of cost of illness studies of influenza outbreaks, expressed in Euros (base year 2017)

Study, (Publication Year)	Setting, year	Perspective	Direct Costs (€, 2017)	Indirect Costs (€, 2017)
Prager et al. (2017)	USA, n/a	Healthcare system, Governmental, Societal	**Seasonal (no vaccination)**: €5.92 billion **Seasonal (vaccination)**: €9.96 billion **Pandemic (no vaccination)**: €81.18 billion **Pandemic (vaccination)**: €65.59 billion	**Illness-related workdays losses** **a) Vaccination and no vaccination in a seasonal scenario:** Vaccination contributes to more workday losses than no vaccination **b) Vaccination and no vaccination in a pandemic scenario**: Vaccination reduces workday losses by 22.2 million days compared to no vaccination
Morales-Suárez-Varela et al. (2016)	Spain, 2009-2010	Healthcare system , Societal	**Total direct cost/patient** Non-pregnant women: €3 908.70 Pregnant women: €2 227.10	**Total indirect cost/patient** Non-pregnant women: €107.18 Pregnant women: €63.83
Silva et al. (2014)	France, 2010-2011	Payer, Societal	**Mean direct cost/patient** All ages – €53.43 0-4 yo – €73.91 5-14 yo – €52.79 15-65 yo – €35.26 ≥65 yo – €44.13 **Total direct costs** All ages – €107 883 835 0-4 yo – €18 908 254 5-14 yo – €52 474 781 15-65 yo – €21 590 741 ≥65 yo – €6 940 836	**Mean daily allowance cost due to work leave/patient** All ages – €22.38 0-4 yo – €0 5-14 yo – €0 15-65 yo – €97.88 ≥65 yo – €0
Higgins et al. (2011)	Australia and New Zealand, 2009	Healthcare system	**Total mean cost**: €19,296,136 Total ICU costs: €6 107 069 Total non-ICU costs: €12 961 942 Mean cost of ICU/patient: €61 368 Mean cost of non-ICU/patient: €10 755 **Mean cost in ICU/per patient and per day**: €4 767	Non-reported
Wilson et al. (2009)	New Zealand, 2009	Healthcare system	**Total ICU costs:** €40 807 660 Median ICU cost/patient: €22 540 Mean ICU cost/patient: €32 168	Non-reported

			Total hospital costs/patient Median hospital cost: €39 696 Mean hospital cost: 53 553 **Treatment costs in ICU per sub-group** a) Cost/patient with and without pre-existing comorbidity €16 100 and €28 980, respectively b) Cost/patient with viral pneumonitis and with other influenza syndromes €22 212 and €12 880, respectively	
Rodríguez-Rieiro et al. (2009)	Spain, 2009	Healthcare system	**Total cost**: €36 700 000 Median cost per hospitalization (concomitant chronic disease) €2 205 Median cost per hospitalization (without a medical condition) €1 172	Non-reported

ICU: intensive care unit, USA: United States of America

1: Confirmed or extrapolated/hypothetical cases on which they base the economic evaluation
*The adjustment was performed from Canadian $, United States $, Australian $, British pounds £ and converted to Euro (Germany has been selected as target currency in these cases) Currencies from European Union countries adjusted to their currency.
*The cost data include all forms of cost derived from inclusion studies, such as overall/total cost, mean/average cost, income loss, labour cost, household cost, savings, cost per case e.t.c.
*For studies without currency year indicated, the previous year of publication was selected for adjustment.

Table 2. Characteristics of full economic evaluation studies on preparedness and response measures of influenza outbreaks, expressed in Euros (base year 2017)

Study, (Publication year)	Setting, Year	Population (n)	Interventions	Comparator	Economic evaluation outcomes
Non-Pharmaceutical studies					
Lankelma et al. (2019)	Netherlands, 2017-2018	Patients with acute RTI at the emergency department (1546 tests, 624 cases)	Point-of-care-testing for Influenza before hospital admission	2016-2017 influenza season	**Net Savings** €388 317 (after subtraction with costs) More than 80% of the total savings are due to the shorter length of stay and decreased hospital admissions. **The overall cost of intervention:** €98 968 Laboratory costs at €72 202 Clinical aspects costs at €26 767
Orset (2018)	France, 2014	200 participants, data extrapolated	7-day home confinement	No intervention	**Costs associated with home confinement** **a) Direct costs** For adults: €742/case For elderly: €1 191/case **b) Indirect costs** **Productivity losses/case** For adults: €550. For elderly: €125 **Costs of death/case** The cost of death for children is estimated at €22-128, for adults at €63-361 and for elderly at €2 667-15 389 **Loss of productivity due to influenza/case** Productivity loss in case of adult sickness: €88.70 (incl. absent from work + reduced productivity) Productivity loss in case of a sick child for the adult (mainly mother): €97.62
Sadique et al. (2008)	UK, 2005	Working parents with depending children	School closure	No intervention	**Cost of school closure:** Between €280 million - €2.8 billion/week **Cost of absenteeism:** €1.4 billion Adjusting for informal care, the cost reduced between €552 - €635 million per week. Adjusting for the elasticity of production the cost reduced to €970 327 320- €1.1 billion per week
Tracht et al. (2012)	USA, (2009-2010 influenza	Simulation of the US (302 million	Population use of face masks (N95) on the spread of a pandemic	No intervention	**Net savings** If masks are worn by 10% of the adult population: €418.75 billion If masks are worn by 50% of the adult population: €501.9 billion

	season)	people:73 million children, 191 million adults, and 38 million seniors)			**Economic burden, if no intervention**: €728.28 billion (incl. direct and indirect costs)
Combined Pharmaceutical and non-Pharmaceutical strategies					
Saunders-Hastings et al. (2017)	Canada, n/a	A simulation of Ottawa, Canada (1.2 million)	**1.**Vaccination + antiviral treatment **2.**Vaccination + antiviral treatment + antiviral prophylaxis **3.** Community contact reduction + personal protective measures + isolation **4.** Community-contact reduction + personal protective measures + isolation + antiviral treatment **5.** School closure + community contact reduction + personal protective measures + quarantine **6.** All interventions	No intervention	**Cost/life-year saved (LYG) Vs no intervention** **1.**€1 700/LYG **2.**€1 769/LYG **3.**€4 394/LYG **4.** €4 447/LYG **5.** €171 590/LYG **6.**€131 679/LYG **Total economic burden** For all scenarios, the economic burden ranges between €75 758 to €1 416 351
Halder et al. (2011)	Australia, 2009	A community in Western Australia (30,000)	Different combinations of durations of individual school closure, antiviral treatment, household antiviral prophylaxis, extended antiviral prophylaxis, 50 % workplace closure, 50% community contact reduction	No intervention	**Cost/case averted:** Antiviral drug strategies + 2 weeks school closure: €396 per case averted (cost-effective) Short-duration school closure: €820/case averted ISC, continuously + 50% workplace. continuously: €6 204/case averted In case of 2 weeks for the above combination: €1 891/case averted ISC, continuously: €2 180/case averted **Total cost, per 100.000 population** The dual strategy of individual school closure for two weeks (ISC) along with the 50% community contact reduction (CCR): €3.39 million The dual strategy of continuous individual school closure (ISC) along with the continuous – 50% workplace closure (WP): €61.3 million. **Productivity loss due to illness and interventions per 100 000 population** ISC (cont.) + WP (cont.): €90.21 million Combined antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis: €4.63
Yarmand et al. (2010)	USA, (2009-2010 influenza	North Carolina State University	Vaccination	Self-Isolation	**High levels of interventions** Self-isolation is incrementally cost-effective than vaccination This has been presented for most of cost ratio values.

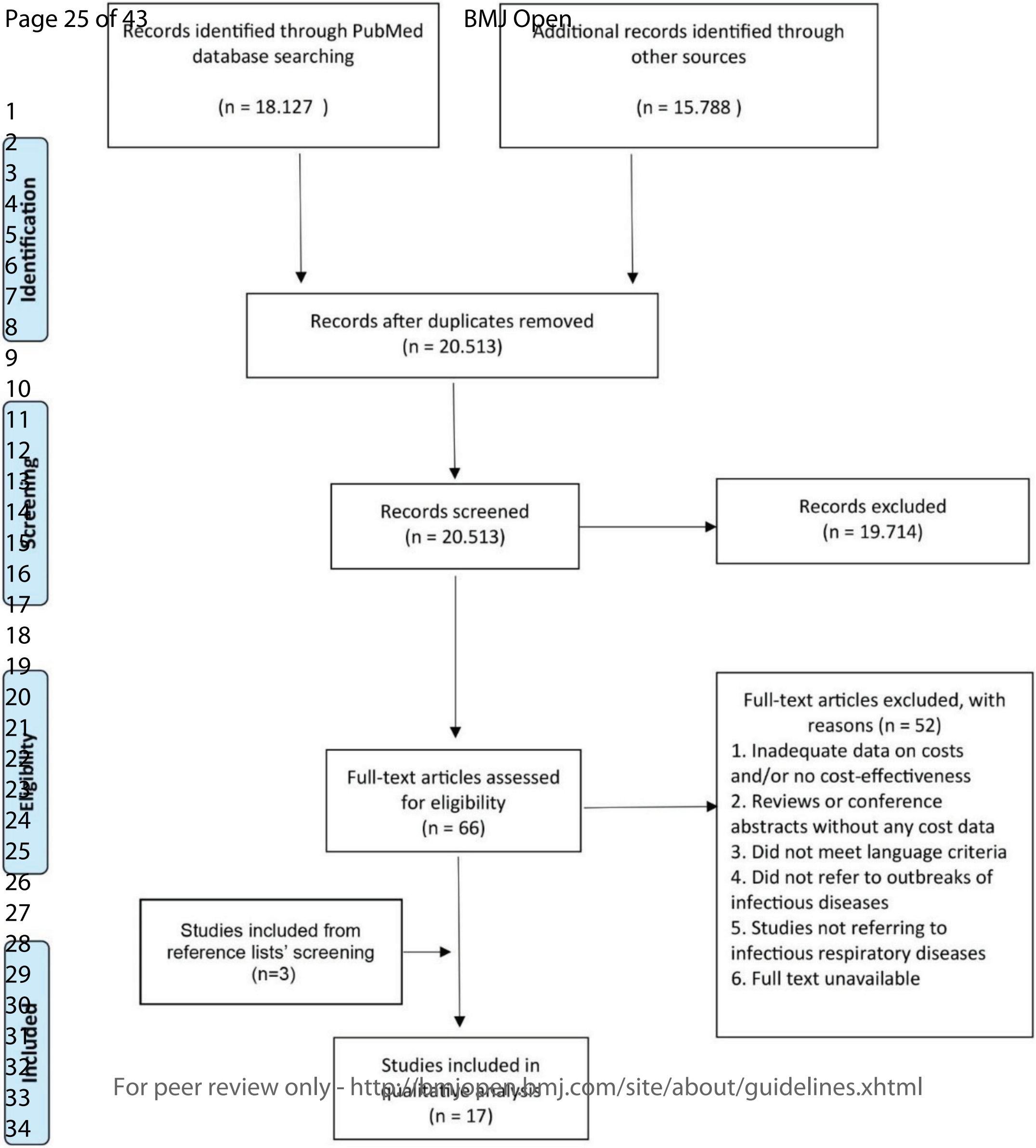
	season)	undergraduate students (23,087)			**Low levels of interventions** Vaccination is incrementally cost-effective than self-isolation The results were robust, even in sensitivity analyses.
Sander et al. (2009)	USA, n/a	Residents of a 1.632-million-person city	**1.** HTAP25 with a stockpile for 25% of the population **2.** HTAP50 with a stockpile for 50% of the population **3.** HTAP with an unlimited stockpile **4.** School closure for 26 weeks **5.** Prevaccination 70% of the population with a low efficacy vaccine **6.** HTAP25 + school closure: **7.** HTAP50 + school closure: **8.** HTAP + school closure: **9.** Prevaccination + school closure: Prevaccinating 70% population with the low-efficacy vaccine, plus closing all schools for 26 weeks **10.** Treatment only: Treating all cases with antivirals **11.** FTAP25 for household contacts and 60% of work/school contacts, stockpile for 25% of the population **12.** FTAP50 for household contacts and 60% of work/school contacts, stockpile for 50% of population **13.** FTAP for household contacts and 60% of work/school contacts, stockpile unlimited **14.** FTAP25 + school closure **15.** FTAP50 + school closure **16.** FTAP + school closure	No intervention	**Cost/capita and cost-effectiveness outcomes** **1**.FTAP is cost-effective (54% reduction attack rate, €119 per capita) **2.** Prevaccination (48% reduction attack rate, €131 per capita) **3.** School closure in combination with each of the above is the least cost-effective (€2 524 per capita) ICUR of FTAP: €42 959 ICUR of prevaccination and school closure: €43 106 **Cost-saving** FTAP and prepandemic vaccination are cost-saving compared to no intervention
Pharmaceutical only strategies					
Khazeni et al. (2009)	USA, n/a	A U.S. metropolitan city (8.3 million)	**1.** Stockpiled strategy **2.** Expanded adjuvanted vaccination **3.** Expanded antiviral prophylaxis	No intervention	**Intervention and treatment costs** 1. Stockpiled strategy: Total cost of €30.1 million and contribution to €288 million treatment costs 2. Expanded adjuvanted vaccination: Total cost of €179 million and contribution to €166 million treatment costs 3. Expanded antiviral prophylaxis: Total cost of €58.4 million and contribution to €266 million treatment costs

					4. No intervention: contribution to €462 million treatment costs **Cost/QALY gained** 1. Stockpiled strategy compared to no intervention: €7 894/QALY 2. Expanded adjuvanted vaccination (at 80% effectiveness) relative to stockpiled strategy: €8 600/QALY 3. Expanded antiviral prophylaxis has a less favourable cost-effectiveness ratio than adjuvanted vaccination Expanded adjuvanted vaccination shown to be a cost-effective intervention because it contributes to 404 030 QALYs at $10 844 per QALY gained relative to stockpiled strategy.
Balicer et al. (2005)	Israel, n/a	Population of Israel (1,618,200 cases/patients)	**Stockpiling with antiviral drugs** **1.**Therapeutic use (all patients) **2.**Therapeutic use (high-risk patients) **3.** Preexposure Long-term prophylaxis (all population) **4.** Preexposure Long-term prophylaxis (high-risk population) **5.** Short-term postexposure prophylaxis for all close contacts	No intervention	**Cost-benefit ratio (CBA)** Therapeutic use (incl. all and high-risk patients): 2.44-3.68 Preexposure (incl. entire and high-risk population): 0.37-0.38 Postexposure: 2.49 Stockpiling with antiviral drugs for high-risk patients remain cost-saving strategy even if the annual probability of a pandemic remains >1 every 80 years. **Overall cost** The overall health-related costs: €56 234 057 The overall cost to the economy: €535 245 986 **Workdays lost due to illness** 6 536 240 or 4 days/patient
Medema et al. (2004)	n/a,	Developed Countries (1 Billion people)	**1.**Egg-based vaccines with 17% population coverage **2.**Cell culture-based vaccines with 37% population coverage	No intervention	**Cost per life-year gained** In general, vaccination is cost-effective. Cell culture-based vaccines: €3 376/LYG (cost-effective) **Cost per intervention** Egg-based: €2.6 billion Cell culture-based: €5.87 billion **Net savings** Egg-based: €8.5 billion Cell culture-based: €5.87 billion Savings: €1.84 billion

CBA: Cost-benefit ratio, LYG: Life-year gained, VSL: Value of statistical life, FTAP: Full targeted antiviral prophylaxis, ISC: Individual school closure, WP: Workplace closure, CCR: Community contact reduction, ICER: Incremental cost-effectiveness ratio, ICUR: Incremental cost-utility ratio; HTAP: Household targeted antiviral prophylaxis

Figure 1. Flowchart

Figure 2. Dominance Ranking Matrix for Pharmaceutical and non-pharmaceutical strategies


Identification
Records identified through PubMed database searching
(n = 18.127)
Additional records identified through other sources
(n = 15.788)
Records after duplicates removed
(n = 20.513)
Screening
Records screened
(n = 20.513)
Records excluded
(n = 19.714)
Eligibility
Full-text articles assessed for eligibility
(n = 66)
Full-text articles excluded, with reasons (n = 52)
1. Inadequate data on costs and/or no cost-effectiveness
2. Reviews or conference abstracts without any cost data
3. Did not meet language criteria
4. Did not refer to outbreaks of infectious diseases
5. Studies not referring to infectious respiratory diseases
6. Full text unavailable
Studies included from reference lists' screening
(n=3)
Included
Studies included in qualitative analysis
(n = 17)

Type of Intervention	Costs*	Health benefit**
Pharmaceutical strategies		
Vaccination as a response measure		
Sander et al. (2009)	–	+
Khazeni et al. (2009)	0	+
Madema et al. (2004)	–	+
Saunders-Hastings et al. (2017)	–	+
General vaccination		
Sander et al. (2009)	–	+
Antiviral drugs		
Sander et al. (2009)	–	+
Halder et al. (2011)	–	+
Balicer et al. (2005)	–	+
Saunders-Hastings et al. (2017)	–	+
Khazeni et al. (2009)	0	+
Stockpile strategy		
Sander et al. (2009)	–	+
Balicer et al. (2005)	–	+
Khazeni et al. (2009)	0	+
Non-Pharmaceutical strategies		
Volunteer isolation		
Orset (2018)	–	+
Saunders-Hastings et al. (2017)	–	+
Pre hospitalisation screening		
Lankelma et al., (2019)	–	+
Community contact reduction		
Saunders-Hastings et al. (2017)	–	+
Halder et al. (2011)	+	+
School closure		
Sadique et al. (2008)	+	+
Saunders-Hastings et al. (2017)	+	+
Halder et al. (2011)	+	+
Sander et al. (2009)	+	+
Personal protective measures		
Tracht et al. (2012)	–	+
Saunders-Hastings et al. (2017)	–	+

**+: the intervention is less cost saving than the comparator; 0: the intervention is equally cost saving with the comparator; -: the intervention is more cost saving than the comparator*

***the intervention is more effective than the comparator; 0: the intervention is equally effective with the comparator; -: the intervention is leff effective than the comparator*

Appendix

Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis: Supplementary Information

Appendix 1. Search concept construction

OVID MEDLINE

Date of Search	OVID Medline		
	#	Search Terms	Hits
29/7/2019	1	Economics/	27061
	2	"costs and cost analysis"/	47439
	3	Cost allocation/	1997
	4	Cost-benefit analysis/	77184
	5	Cost control/	21373
	6	Cost savings/	11287
	7	Cost of illness/	25397
	8	Cost sharing/	2443
	9	"deductibles and coinsurance"/	1716
	10	Medical savings accounts/	529
	11	Health care costs/	37249
	12	Direct service costs/	1171
	13	Drug costs/	15395
	14	Employer health costs/	1088
	15	Hospital costs/	10427
	16	Health expenditures/	18983
	17	Capital expenditures/	1987
	18	Value of life/	5653
	19	exp economics, hospital/	23708
	20	exp economics, medical/	14108
	21	Economics, nursing/	3989
	22	Economics, pharmaceutical/	2874
	23	exp "fees and charges"/	29802
	24	(low adj cost).mp.	51166
	25	(high adj cost).mp.	13286
	26	(health?care adj cost$).mp.	10352
	27	(fiscal or funding or financial or finance).tw.	136748
	28	(cost adj estimate$).mp.	2132
	29	(cost adj variable).mp.	42
	30	(unit adj cost$).mp.	2368
	31	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	277405
	32	Economic evaluation.mp.	9144
	33	(Cost?effectiveness analysis or CEA).mp.	21933
	34	(Cost?utility analysis or CUA).mp.	1153
	35	(Cost?benefit analysis or CBA).mp.	26471
	36	(Cost?consequence analysis or CCA).mp.	7687
	37	(Cost?minimi?sation analysis or CMA).mp.	3583
	38	(cost?outcome or marginal analysis).mp.	204
	39	exp Cost benefit analysis/ or exp budgets/	90077
	40	investment$.mp. or investments/	39609
	41	or/1-40	769608
	42	exp Emergency Preparedness/	2678
	43	exp Preparedness, Emergency/	2678
	44	(Community Preparedness or Community Recovery or Emergency Operations Coordination or (Emergency Public Information and Warning) or Fatality Management or Information Sharing or Mass Care or Medical Countermeasure Dispensing or (Medical Materiel Management and Distribution)	2614

		or Medical Surge or Non-Pharmaceutical Interventions or Public Health Laboratory Testing).mp.	
	45	exp Public Health Surveillance/	2623
	46	(Epidemiological Investigation or (Responder Safety adj Health) or Volunteer Management).mp.	2867
	47	(disaster preparedness or public health emergencies).mp.	2012
	48	((Detection adj assessment) or policy development or policy implementation or policy adaptation or health services or (coordination adj communication) or emergency risk communication or personal preparedness).mp.	393599
	49	((state or local or national or legal or business or healthcare) and preparedness).mp.	4359
	50	(vaccination or immuni?ation or anti?viral medication or personal hygiene or hand hygiene or household ventilation or ((food and safety) or storage) or food hygiene or respiratory etiquette or (washing and saniti?ing) or social distancing or triage or food security or (emergency adj3 food) or (school adj3 closure) or public gathering* or public meeting* or household isolation or quarantine or PPE or personal protective equipment or (environmental adj3 cleaning)).mp.	545475
	51	or/42-50	940853
	52	exp disease outbreak/ or exp communicable diseases/	119498
	53	(disease outbreak or outbreak or epidemic or pandemic or public health emergency).mp.	150101
	54	(avian flu or abola or EVD or H1N1 or H5N1 or infectious disease or influenza or swine flu or flu or MERS or Middle East Respiratory Syndrome).mp.	165207
	55	(SARS or Severe Acute Respiratory syndrome or measles or zika or cholera or H7N9 or dengue or fever or plague or fever or malaria or polio).mp.	381260
	56	(Bacillus cereus or Campylobacter jejuni or Clostridium or Cryptosporidium or Cyclospora cayetanensis or (E adj coli) or Hepatitis A or Listeria monocytogenes or Noroviruses or Salmonella or Shigella or Staphylococcus aureus or Staphylococcus or Vibrio parahaemolyticus or Vibrio vulnificus).mp.	493801
	57	(Diphtheria or Haemophilus influenzae type b or Hib or Hepatitis B or Human Papillomavirus or HPV).mp.	165778
	58	((Meningococcal adj Infection$) or Mump$ or Pertussis or Whooping Cough or Pneumococcal Infection$ or Polio or Rotavirus or Rubella or German Measles or Tetanus or varicella or chicken pox or vectorbourne diseases or vector?bourne disease$ or waterbourne diseases or water?bourne disease$ or Cholera or Diarrhea or diarrhoea).mp.	255768
	59	(Typhoid fever or Giardiasis or Schistosomiasis or Dracunculiasis or Dysentery or Cryptosporidiosis or amoebiasis or Traveler$s diarrhea or travelers diarrhoea).mp.	68954
	60	exp infectious disease medicine/ or exp malaria/ or exp influenza, human/ or SARS virus/ or exp norovirus/ or exp coronavirus infections/ or exp measles/ or exp poliomyelitis/ or exp chickenpox/	165698
	61	(anthrax or botulism or brucellosis or campylobacter enteritis or chikungunya or chlamydia$ or CJD or Creutzfeldt?Jakob).mp.	63613
	62	(diptheria or echinococcosis or gonococcal or haemophilus influenzae or hepatitis or HIV or AIDS or human immunodeficiency virus or acquired immunodeficiency syndrome).mp.	714394
	63	(legionnaires?disease or leptospirosis or listeriosis or lyme or streptococcus pneumoniae or Q fever or rabies or congenital rubella or salmonella or shiga toxin or verocytotoxin?producing E?coli or STEC or VTEC or HUS or haemoltic?uraemic or hemoltic?uremic).mp.	182938
	64	(shigellosis or smallpox or syphilis or congenital syphilis or tick?borne viral encephalitis or congenital toxoplasmosis or	341238

		trichinellosis or tuberculosis or TB or typhoid or paratyphoid or VHF or viral hemorrhagic fever$ or viral haemorrhagic fever$ or West Nile virus or Yellow fever or (enteritis adj3 yersinia)).mp.	
	65	or/52-64	2357602
	66	41 and 51 and 65 (studies before 2003 excluded)	18127

EMBASE

Date of Search	EMBASE		
	#	**Search Terms**	**Hits**
29/7/2019	1	Socioeconomics/	133589
	2	Cost benefit analysis/	81690
	3	Cost effectiveness analysis/	143890
	4	Cost of illness/	18428
	5	Cost control/	65812
	6	Economic aspect/	110246
	7	Financial management/	110636
	8	Health care cost/	181209
	9	Health care financing/	13089
	10	Health economics/	32080
	11	Hospital cost/	20343
	12	(fiscal or financial or finance or funding).tw.	178545
	13	Cost minimization analysis/	3375
	14	(cost adj estimate$).mp.	3181
	15	(cost adj variables$).mp.	188
	16	(unit adj cost$).mp.	4210
	17	investment$.mp. or investments/	49607
	18	or/1-17	906830
	19	"Emergency Preparedness".tw.	1780
	20	(Community Preparedness or Community Recovery or Emergency Operations Coordination or (Emergency Public Information and Warning) or Fatality Management or Information Sharing or Mass Care or Medical Countermeasure Dispensing or (Medical Materiel Management and Distribution) or Medical Surge or Non-Pharmaceutical Interventions or Public Health Laboratory Testing).mp.	3358
	21	exp Public Health Surveillance/	210835
	22	(Epidemiological Investigation or (Responder Safety adj Health) or Volunteer Management).mp.	3638
	23	(disaster preparedness or public health emergencies).mp.	2176
	24	((Detection adj assessment) or policy development or policy implementation or policy adaptation or health services or (coordination adj communication) or emergency risk communication or personal preparedness).mp.	124325
	25	((state or local or national or legal or business or healthcare) and preparedness).mp.	5302
	26	(vaccination or immuni?ation or anti?viral medication or personal hygiene or hand hygiene or household ventilation or ((food and safety) or storage) or food hygiene or respiratory etiquette or (washing and saniti?ing) or social distancing or triage or food security or (emergency adj3 food) or (school adj3 closure) or public gathering* or public meeting* or household isolation or quarantine or PPE or personal protective equipment or (environmental adj3 cleaning)).mp.	703894
	27	or/19-26	1031364

	28	exp disease outbreak/ or exp communicable diseases/	119087
	29	(disease outbreak or outbreak or epidemic or pandemic or public health emergency).mp.	207717
	30	(avian flu or abola or EVD or H1N1 or H5N1 or infectious disease or influenza or swine flu or flu or MERS or Middle East Respiratory Syndrome).mp.	198862
	31	(SARS or Severe Acute Respiratory syndrome or measles or zika or cholera or H7N9 or dengue or fever or plague or fever or malaria or polio).mp.	561066
	32	(Bacillus cereus or Campylobacter jejuni or Clostridium or Cryptosporidium or Cyclospora cayetanensis or (E adj coli) or Hepatitis A or Listeria monocytogenes or Noroviruses or Salmonella or Shigella or Staphylococcus aureus or Staphylococcus or Vibrio parahaemolyticus or Vibrio vulnificus).mp.	579612
	33	(Diphtheria or Haemophilus influenzae type b or Hib or Hepatitis B or Human Papillomavirus or HPV).mp.	241684
	34	((Meningococcal adj Infection$) or Mump$ or Pertussis or Whooping Cough or Pneumococcal Infection$ or Polio or Rotavirus or Rubella or German Measles or Tetanus or varicella or chicken pox or vectorbourne diseases or vector?bourne disease$ or waterbourne diseases or water?bourne disease$ or Cholera or Diarrhea or diarrhoea).mp.	421975
	35	(Typhoid fever or Giardiasis or Schistosomiasis or Dracunculiasis or Dysentery or Cryptosporidiosis or amoebiasis or Traveler$s diarrhea or travelers diarrhoea).mp.	56723
	36	exp infectious disease medicine/ or exp malaria/ or exp influenza, human/ or SARS virus/ or exp norovirus/ or exp coronavirus infections/ or exp measles/ or exp poliomyelitis/ or exp chickenpox/	213621
	37	(anthrax or botulism or brucellosis or campylobacter enteritis or chikungunya or chlamydia$ or CJD or Creutzfeldt?Jakob).mp.	78479
	38	(diptheria or echinococcosis or gonococcal or haemophilus influenzae or hepatitis or HIV or AIDS or human immunodeficiency virus or acquired immunodeficiency syndrome).mp.	938033
	39	(legionnaires?disease or leptospirosis or listeriosis or lyme or streptococcus pneumoniae or Q fever or rabies or congenital rubella or salmonella or shiga toxin or verocytotoxin?producing E?coli or STEC or VTEC or HUS or haemoltic?uraemic or hemoltic?uremic).mp.	206207
	40	(shigellosis or smallpox or syphilis or congenital syphilis or tick?borne viral encephalitis or congenital toxoplasmosis or trichinellosis or tuberculosis or TB or typhoid or paratyphoid or VHF or viral hemorrhagic fever$ or viral haemorrhagic fever$ or West Nile virus or Yellow fever or (enteritis adj3 yersinia)).mp.	313309
	41	or/28-40	2651637
	42	18 and 27 and 41 (studies before 2003 excluded)	14223

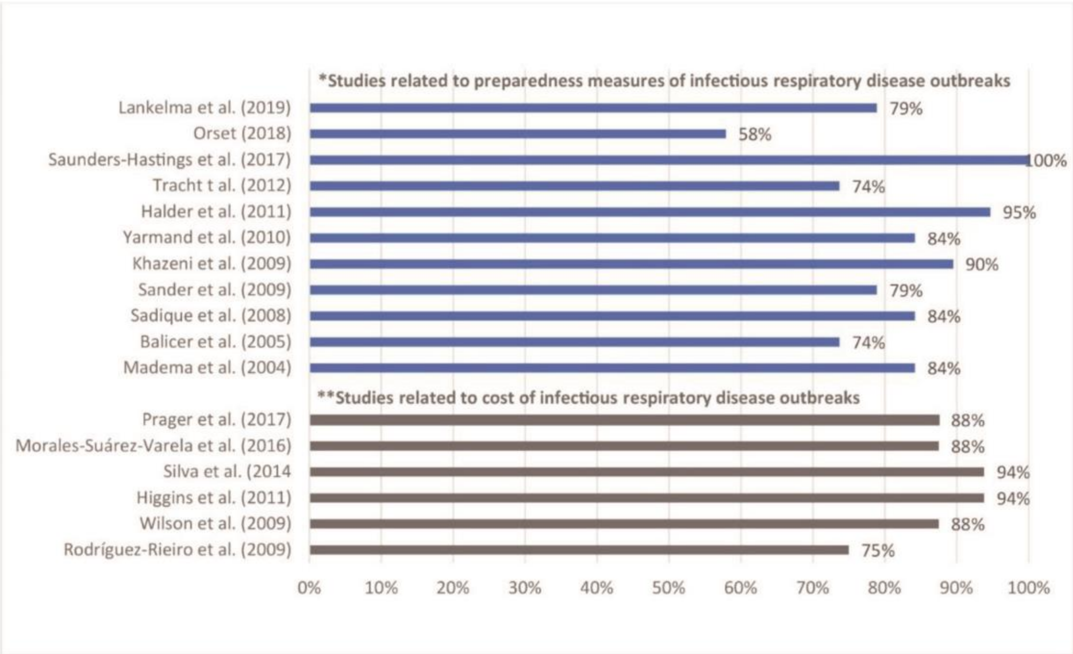
ECONLIT

Date of Search	EconLit		
	#	Search Terms	Hits
30/8/2019	1	cost OR (deductibles and coinsurance) OR Medical savings accounts OR health expenditure OR economic OR (fees and charges) OR Economic evaluation OR cost effectiveness analysis OR Cost utility analysis OR cost benefit analysis OR Cost consequence analysis OR Investment	1,344,466
30/8/2019	2	(Emergency Preparedness) OR Preparedness OR emergency OR Surveillance OR disaster OR (detection or diagnosis or identification or early detection) OR screening OR vaccination OR hygiene OR school closure OR quarantine	48,619
30/8/2019	3	disease outbreak OR disease OR infectious diseases OR communicable diseases OR outbreak OR pandemic OR epidemic	9,194
31/8/2019	4	S1 AND S2 AND S3 (limitation: from 2003 to 2019)	965

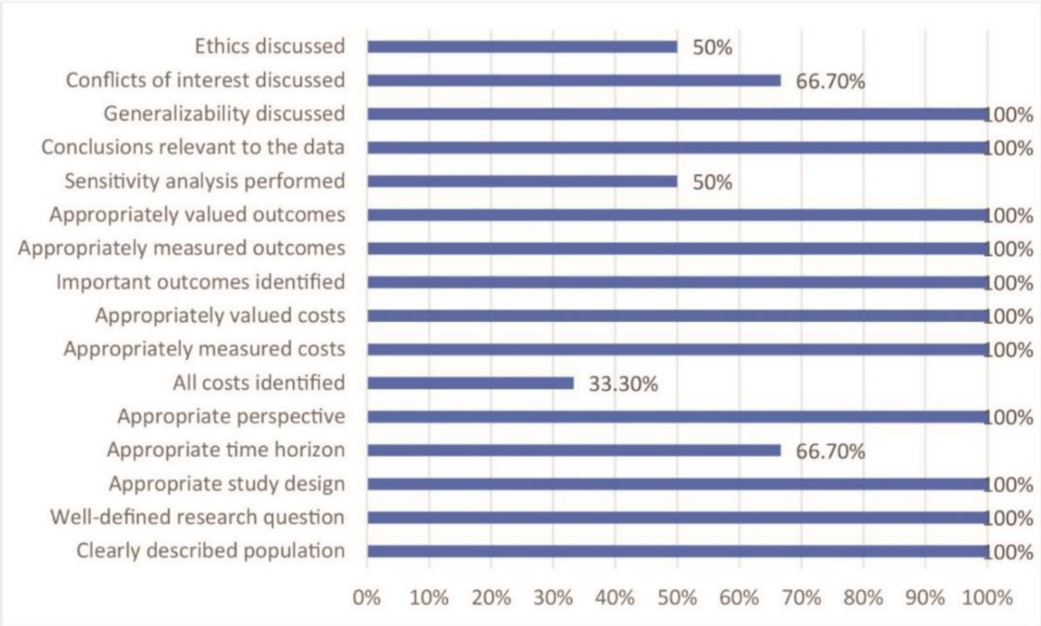
IDEAS REPEC

Date of Search	IDEAS REPEC			
	Search Term 1	Search Term 2	Search Term 3	Results (n)
28/7/2019	cost-effective	infectious		139
28/7/2020	Emergency Public Information and Warning	cost		8
28/7/2021	Health Surveillance	infectious	cost	10
30/7/2022	economics	health preparedness		39
30/7/2023	cost-effectiveness	cost effectiveness	health preparedness	8
30/7/2024	prevention	cost	disease outbreaks	42
30/7/2025	economic evaluation	Public health surveillance		12
30/7/2026	investment	Infectious disease	outbreak	16
30/7/2027	economics	H1N1		16
30/7/2028	economics	flu	outbreak	25
1/8/2019	Cost-effectiveness	ebola		4
1/8/2019	economics	disease threats		171
1/8/2019	pandemic	economic	cost	42

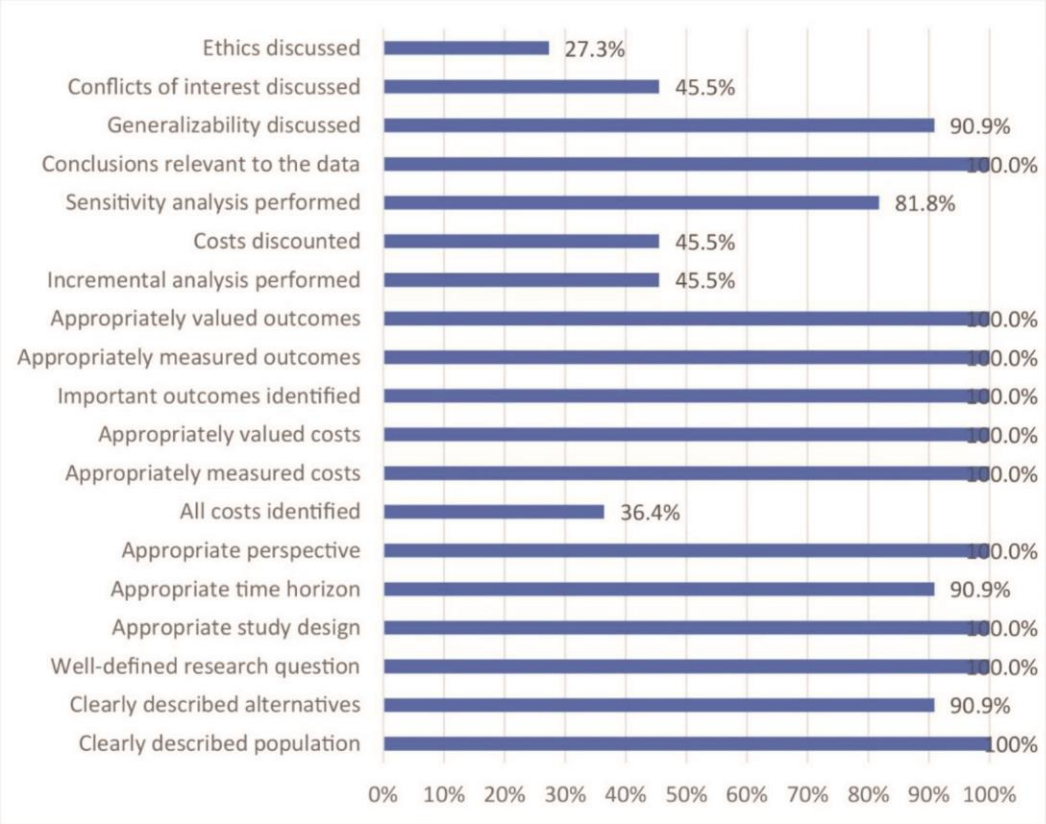
Appendix 2. Total quality appraisal score (in percentages) for all included studies (n=17)



Appendix 3. Quality appraisal score by item/question for the partial economic evaluation studies (n=6)



Appendix 4. Quality appraisal by item/question of the full evaluation studies (n=11)



Appendix 5. Characteristics of cost analyses studies of influenza outbreaks

Study, (Publication Year)	Setting, year	Study population (n)	Economic Evaluation	Approach	Perspective	Time Horizon	Type of Sensitivity analysis
Prager et al. (2017)	USA, n/a	The population of the USA	Cost of illness (although mentions about cost-effective of vaccination in the pandemic scenario, No CEA outcomes)	Simulation model	Healthcare system, Governmental, Societal	Not clearly stated	Performed, unclear
Morales-Suárez-Varela et al. (2016)	Spain, 2009-2010	Unvaccinated women of childbearing age with influenza A (H1N1)	Partial Economic Evaluation (Cost of illness)	Observational	Healthcare system, Societal	4 months	Not performed
Silva et al. (2014)	France, 2010-2011	Population with Influenza B (201)	Partial Economic Evaluation (cost of illness)	Observational	Payer, Societal	3 months	One-way sensitivity analysis and probabilistic analysis
Higgins et al. (2011)	Australia and New Zealand, 2009	All Influenza cases (H1N1) in New Zealand and Australia (762)	Partial Economic Evaluation Cost of illness	Observational	Healthcare system	3 months	Not performed
Wilson et al. (2009)	New Zealand, 2009	All Influenza hospitalisations in New Zealand) 1224 – 1122 hospitalizations and + 122 ICU	Partial Economic Evaluation, Cost of illness (incl. hypothetical cost-effectiveness analysis)	Observational	Healthcare system	12 months	Probabilistic sensitivity analysis
Rodríguez-Rieiro et al. (2009)	Spain, 2009	All Spanish patients with H1N1 (11,449)	Partial Economic Evaluation (Cost of illness)	Observational	Healthcare system	12 months	Not performed

Appendix 6. Characteristics of studies on preparedness and response measures of influenza outbreaks

Study, (Publication year)	Setting, Year	Population (n)	Economic Evaluation Approach	Perspective	Timeframe	Discount	Sensitivity analysis
Observational studies							
Lankelma et al. (2019)	Netherlands, 2017-2018	Patients with acute RTI at the emergency department (1546 tests, 624 cases)	Partial Economic Evaluation	Healthcare system	4,5 months	N/A	Not performed
Sadique et al. (2008)	UK, 2005	Working parents with depending children	Partial Economic Evaluation	Societal	1 year	N/A	Scenarios
Simulation or mathematical models							
Orset (2018)	France, 2014	200 participants, data extrapolated	Both cost-benefit and cost-effectiveness analysis	Public health and societal	1 year	1% for costs	Not performed
Saunders-Hastings et al. (2017)	Canada, n/a	A simulation of Ottawa, Canada (1.2 million)	cost-effectiveness analysis	Healthcare system	Lifetime	1.5%	Multivariate sensitivity analyses
Halder et al. (2011)	Australia. 2009	A community in Western Australia (30,000)	cost-effectiveness analysis	Healthcare and Societal	Lifetime	3%	Scenarios
Tracht et al. (2012)	USA, (2009-2010 influenza season)	Simulation of the US (302 million people:73 million children, 191 million adults, and 38 million seniors)	cost-effectiveness analysis	Healthcare system and societal	1 year	N/A	Multivariate sensitivity analyses
Yarmand et al. (2010)	USA, (2009-2010 influenza season)	North Carolina State University undergraduate students (23,087)	cost-effectiveness analysis	Healthcare system	5 months	N/A	One-way and two-way sensitivity analyses
Sander et al. (2009)	USA, n/a	Residents of a 1 632-million-person city	Cost Utility Analysis	Societal	6 months	3%	Multivariate sensitivity analyses
Khazeni et al. (2009)	USA, n/a	A U.S. metropolitan city (8.3 million)	cost-effectiveness analysis	Societal	Lifetime	3% for benefits/ costs	Monte Carlo probabilistic sensitivity analysis
Balicer et al. (2005)	Israel, n/a	Population of Israel (1 618 200 cases)	Cost-benefit analysis	Healthcare system Societal	Lifetime	Not specified	Multivariate sensitivity analyses
Medema et al. (2004)	UK, Germany, Netherlands, (2004)	Developed Countries (1 Billion people)	Cost-effectiveness analysis	Healthcare system	Not clearly stated	5%	Performed unclear

RTI: Acute respiratory tract infection, N/A: Not applicable, UK: United Kingdom, US: United States

Appendix 7. Comparative analysis of health indexes when averting/responding to respiratory disease outbreaks

Study / year	Intervention(s)/Screening methods vs. comparators	Outcomes/benefits
Prager et al. 2016	Case 1: No Vaccination, Seasonal Outbreak Case 2: No Vaccination, Pandemic Outbreak Vs. Case 3: Vaccination, Seasonal Outbreak Case 4: Vaccination, Pandemic Outbreak	**Productivity loss and behavioural response** **In the case of a pandemic influenza outbreak** Vaccination: 1. Reduces illness-related workday losses from 83.3 million days to 61.1 million days (a reduction of 22.2 million days). 2. Causes 7.4 million days of workday losses due to the time that people spend on getting the vaccination doses. 3. Can reduce public avoidance behaviours by 25%. **In the case of a seasonal influenza outbreak** Vaccination: 1. Reduces illness-related workday losses from 18.7 million days to 13.9 million days (a reduction of 4.8 million days). 2. Causes 6.7 million days of workday losses due to the time that people spend obtaining vaccinations. 3. Can reduce public avoidance behaviours by 25%.
Medema et al. 2004	1. Egg-based vaccine manufacture 2. Cell culture-based vaccine manufacture Vs. No intervention	**Cases, PCP consultations and hospitalizations prevented** **Cell culture-based intervention vs no intervention:** Cell culture-based intervention avoids 75 million influenza cases, 3.78 million PCP consultations for influenza treatment and, respectively, 5.81 million and 1.21 million influenza-related hospitalizations and excess deaths. **Egg-based vaccine intervention vs no intervention:** Egg-based vaccine intervention leads to vaccination of 17% of the population, which avoids 29.8 million influenza cases, 1.74 million PCP visits, 2.67 million hospitalizations and 556 000 deaths **Cell culture-based intervention vs egg-based vaccine intervention with 17% vaccine coverage:** Cell culture-based intervention strategy leads to vaccination of 37% of the population, avoiding an additional 35 million influenza cases, 2.04 million PCP consultations for influenza treatment, 3.14 million influenza-related hospitalizations and 654 500 excess deaths **Years of life lost (YLL)** Cell culture-based intervention strategy: 2.56 million

Saunders-Hastings et al. 2017	1. Vaccination and antiviral treatment 2. Vaccination, antiviral treatment and antiviral prophylaxis 3. Community-contact reduction, personal protective measures and voluntary isolation 4. Community-contact reduction, personal protective measures, voluntary isolation and antiviral treatment 5. School closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine 6. All interventions Vs. 7. No intervention	**Hospitalizations** In case of no intervention, a total of 2 472 pandemic-associated hospitalizations have been estimated. Following no intervention, vaccination interventions (combined with other interventions) contributed to 765-815 hospitalizations. Last, school closure, combined with other interventions, contributed to 108-550 hospitalizations. **YLL** 1. 3,026 2. 2,801 3. 1,767 4. 1,607 5. 1,393 6. 267 7. 9,421 **Reductions of illness (H2N2 cases)** Vaccination, personal protective measures, combined voluntary isolation and quarantine procedures resulted in the greatest reductions, producing attack rates of 50.0%, 45.5% and 33.9%, respectively. Antiviral treatment, antiviral prophylaxis, school closure and community-contact reduction produced only small reductions in illness attack rate, whether implemented alone or in combination with other interventions. Even in the absence of any pharmaceutical intervention, adherence to rigorous non-pharmaceutical protocols -school closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine-resulted in a reduction of the illness attack rate to 15.2%,
Khazeni et al. 2009	1) Vaccination and antiviral pharmacotherapy in quantities similar to those currently available in the U.S. stockpile (stockpiled strategy), 2) Stockpiled strategy but with the expanded distribution of antiviral agents (expanded prophylaxis strategy), and 3) Stockpiled strategy but with the adjuvanted vaccine (expanded vaccination strategy). Vs. no intervention	**Clinical attack rate** The clinical attack rate has been 11%, 17%, 19% and 33% for expanded adjuvanted vaccination, expanded antiviral prophylaxis, Stockpiled strategy and for no intervention, respectively. **Deaths averted** Expanded adjuvanted vaccination – 45 941 deaths averted Expanded antiviral prophylaxis – 32 745 deaths averted Stockpiled strategy – 29 761 deaths averted No intervention - No deaths averted
Sander et al.	1. HTAP25 with a stockpile for 25% of the population 2. HTAP50 with a stockpile for 50% of the population 3. HTAP with an unlimited stockpile	**QALYs gained, total** Expanded adjuvanted vaccination – 404 030 total QALYs gained Expanded antiviral prophylaxis – 282 329 total QALYs gained

2009	4. School closure for 26 weeks 5. Prevaccination 70% of the population with a low efficacy vaccine 6. HTAP25 + school closure: 7. HTAP50 + school closure: 8. HTAP + school closure: 9. Prevaccination + school closure: Prevaccinating 70% population with the low-efficacy vaccine, plus closing all schools for 26 weeks 10. Treatment only: Treating all cases with antivirals 11. FTAP25 for household contacts and 60% of work/school contacts, stockpile for 25% of the population 11. FTAP50 for household contacts and 60% of work/school contacts, stockpile for 50% of population 12. FTAP for household contacts and 60% of work/school contacts, stockpile unlimited 14. FTAP25 + school closure 13. 15. FTAP50 + school closure 14. 16. FTAP + school closure	Stockpiled strategy – 258 342 total QALYs gained No intervention - No QALYs gained **QALYs per 1000 population, total** All interventions gained a similar amount of QALYs, with some differences between them (21,141 for no intervention to 21 403 for prevaccination and school closure). Compared to FTAP not involving school closure, FTAP plus school closure or prevaccination plus school closure gains 51 QALYs **QALYs per 1000 population, incremental** FTAP and school closure and the intervention of prevaccination and school closure contributed to the most incremental QALYs (262) **Deaths per 1000 population** Pre-vaccination intervention was the most effective strategy. Only 1 death/1000 population occurred via this strategy. On the other side, most deaths have been seen in case of no intervention (13 deaths/1000 population) and FTAP25 with 12 deaths. **Number of cases** Full TAP is the most effective single strategy, reducing the number of cases by 54% Pre-vaccination reduces the number of cases by 48% Adding school closure to full TAP or pre-vaccination further improves health outcomes
Yarmand et al. 2010	Self-isolation and mandatory quarantine Vs. vaccination	**Effectiveness in low-levels of interventions** Vaccination is more effective than self-isolation. **Effectiveness in high-levels of interventions** Self-isolation is more effective than vaccination. This has been shown due to weaknesses of vaccinations, such as delays in effectiveness.
Halder et al. 2011	Antiviral drugs combined with limited duration school closure Vs. 1. School closure as a sole intervention alone and as dual, triple, quadruple strategy 2. Other social distancing strategies, such as reduced workplace attendance	**The illness attack rate of interventions (symptomatic)** The illness attack rate ranges from 2.4% (SD 0.37) to 8.5% (SD 1.1) while that of the unmitigated attack rate is 13% (SD 0.9). The individual school closure for 2 weeks along with the continuous – 50% workplace closure, antiviral treatment, household antiviral prophylaxis and extended antiviral prophylaxis showed the lowest illness attack rate (2.4%). This combination is the most effective intervention. Short-duration school closure is less effective (6.5 to 8.2 illness attack rate) Continuous school closure is more effective, with an attack rate of 3.2.

Orset 2018	Home confinement Vs. No intervention	**Incidence rate reduction by the home confinement intervention** There are studies that indicate the higher the compliance rate regarding home confinement, the higher the reduction of the incidence rate of influenza will be. More particularly: In case of a 70% compliance rate: 83% reduction of incidence rate In the case of 80% compliance rate: 91% reduction of incidence rate The compliance rate with home confinement is between 75.90 and 94.44%, for this study. **Rate reduction threshold in the incidence due to intervention** The higher the proportion of all cases complying with home confinement, the higher the reduction rate of the threshold for VSL will be. For example: In case of 49.24% of all cases complying with home confinement: €7.65 million Threshold for VSL In case of 51.39% of all cases complying with home confinement: €5.06 million Threshold for VSL
Trach t t al. 2012	Mask wearing group Vs. No intervention	**When there are no interventions (no masks worn)** **Cumulative number of cases/ based on three scenarios - R avg/unc*** In the case of 1.25; A total of 101,424,384 cases. Most of them identified at 18-64 age group. In the case of 1.3; A total of 117 673 024 cases. Most of them identified at 18-64 age group. In the case of 1.35; A total of 130 043 351 cases. Most of them identified at 18-64 age group. **Hospitalizations** Based on three different scenarios - R avg/unc: 1.25, 1.3, and 1.35 In the case of 1.25: For all age groups, a total of 3 275 616 hospitalizations have been estimated. 75.8% of them found to be in 18-64 ages In the case of 1.3: For all age groups, a total of 3 793 350 hospitalizations have been estimated. 74.8% of them found to be in 18-64 ages In the case of 1.35: For all age groups, a total of 4 184 352 hospitalizations have been estimated. 73.7% of them found to be in 18-64 ages **Deaths** More deaths have been found in ages 18-64, both in three scenarios, and more than 90% of the total deaths (281 319-349 578)

		As a result, the model showed that in case of 10% of the population wearing masks with an effectiveness of 20% in reducing susceptibility and infectivity, there is a large reduction in the cumulative number of cases.

PCP: Primary care physician, YLL: Yearls of life lost, VSL: Value of statistical life, QALY: Quality-adjusted life year, FTAP: Full-targeted antiviral prophylaxis, SD: Standard deviation,

* Average effective reproduction number (uncontrolled)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary, Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary, Appendix 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary, Appendix 2,3,4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary, Appendix 2,3,4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

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doi:10.1371/journal.pmed1000097

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